AMERICAN PRACTITIONER

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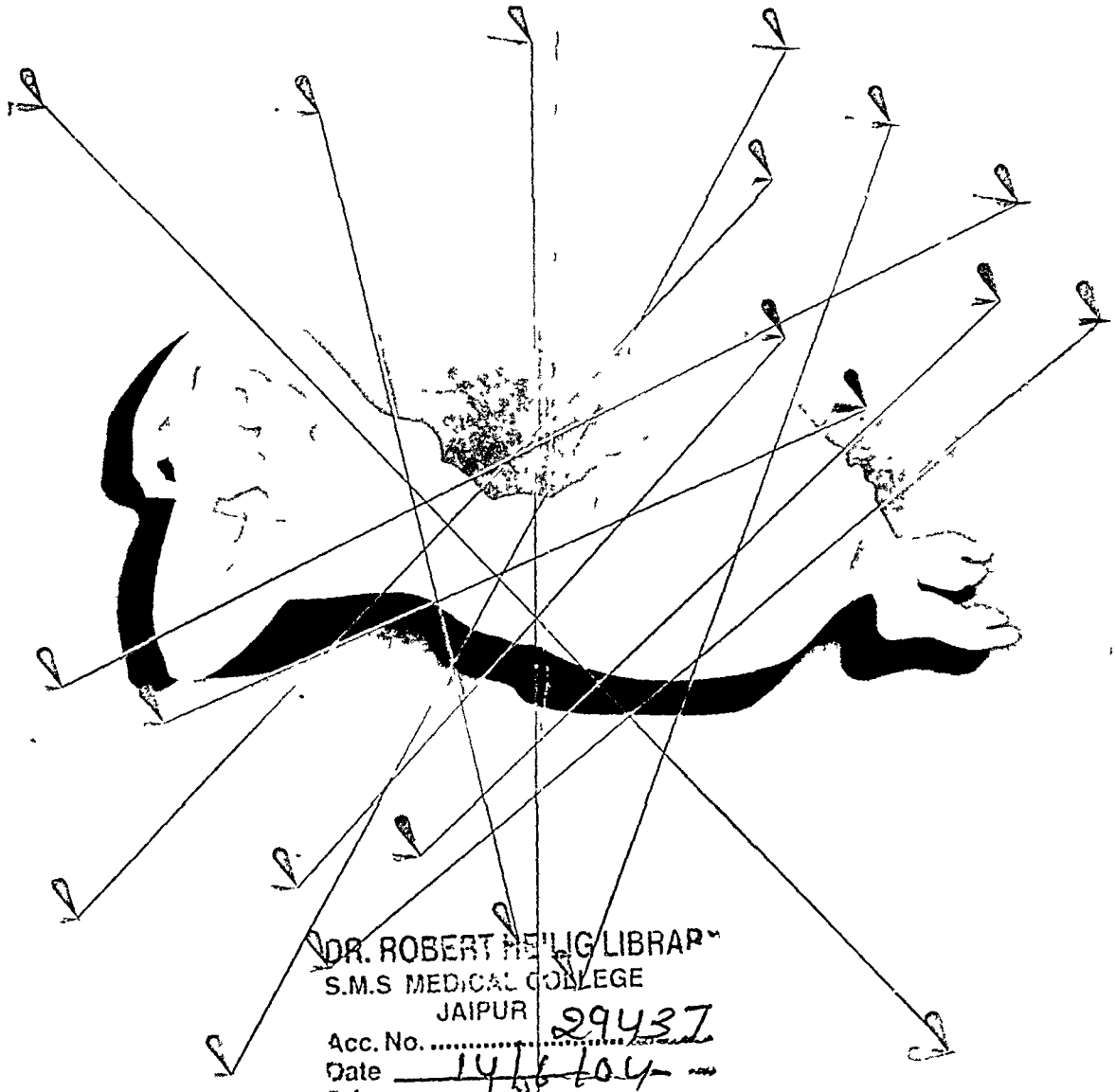
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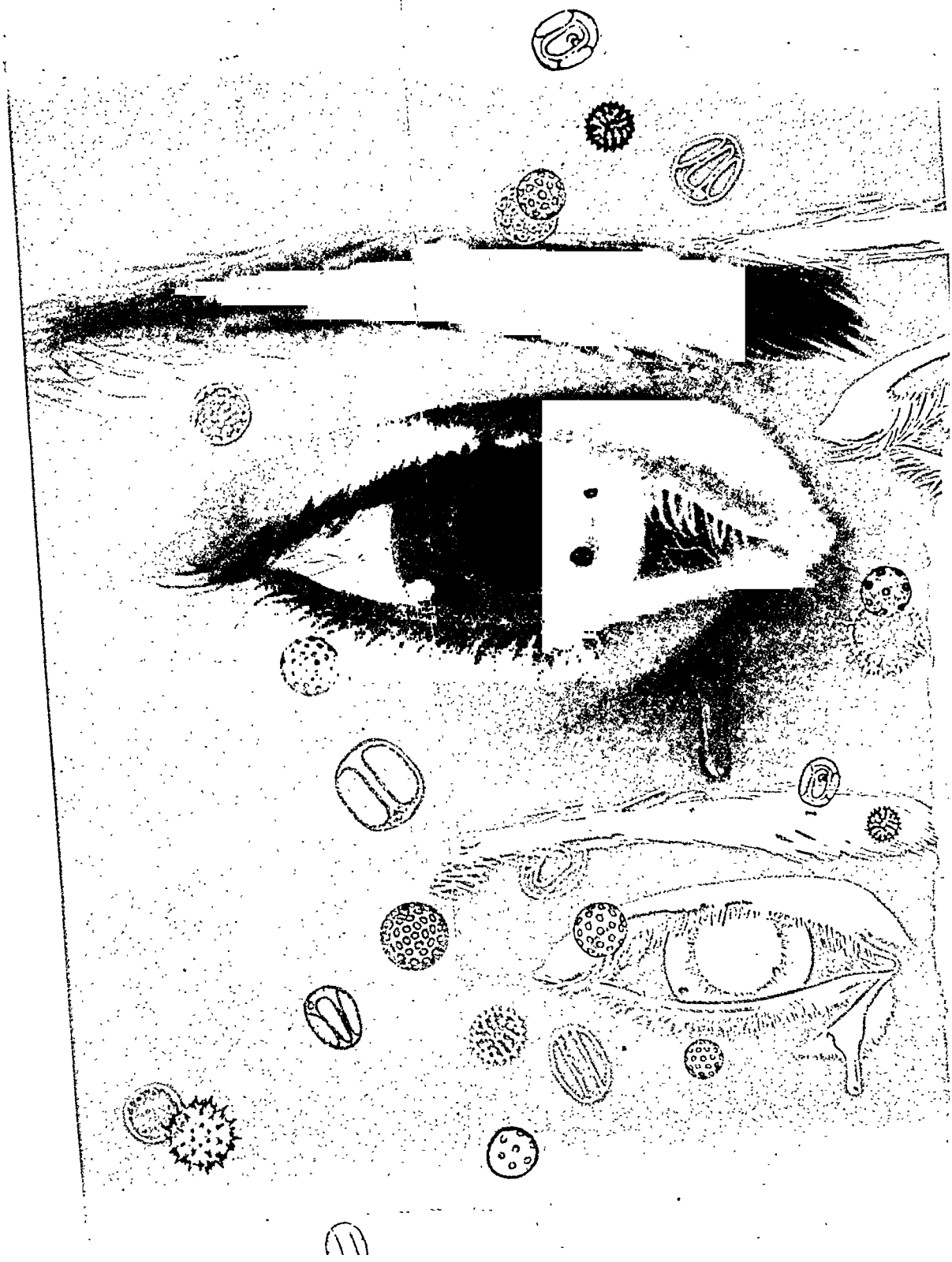
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ıered as second class matter September 26, 1946, at the Philadelphia, Pa., Post Office, under the Act of March 3, 1879. Additional ry at Lancaster, Pa. Subscription $10.00 per year in U. S. funds; postpaid in the United States and Pan American Postal Union, eign postage $1.00 extra. Canada $11.00. Copyright 1947 by J. B. Lippincott Company, 227–231 South Sixth Street, Philadelphia. d in U. S. A.



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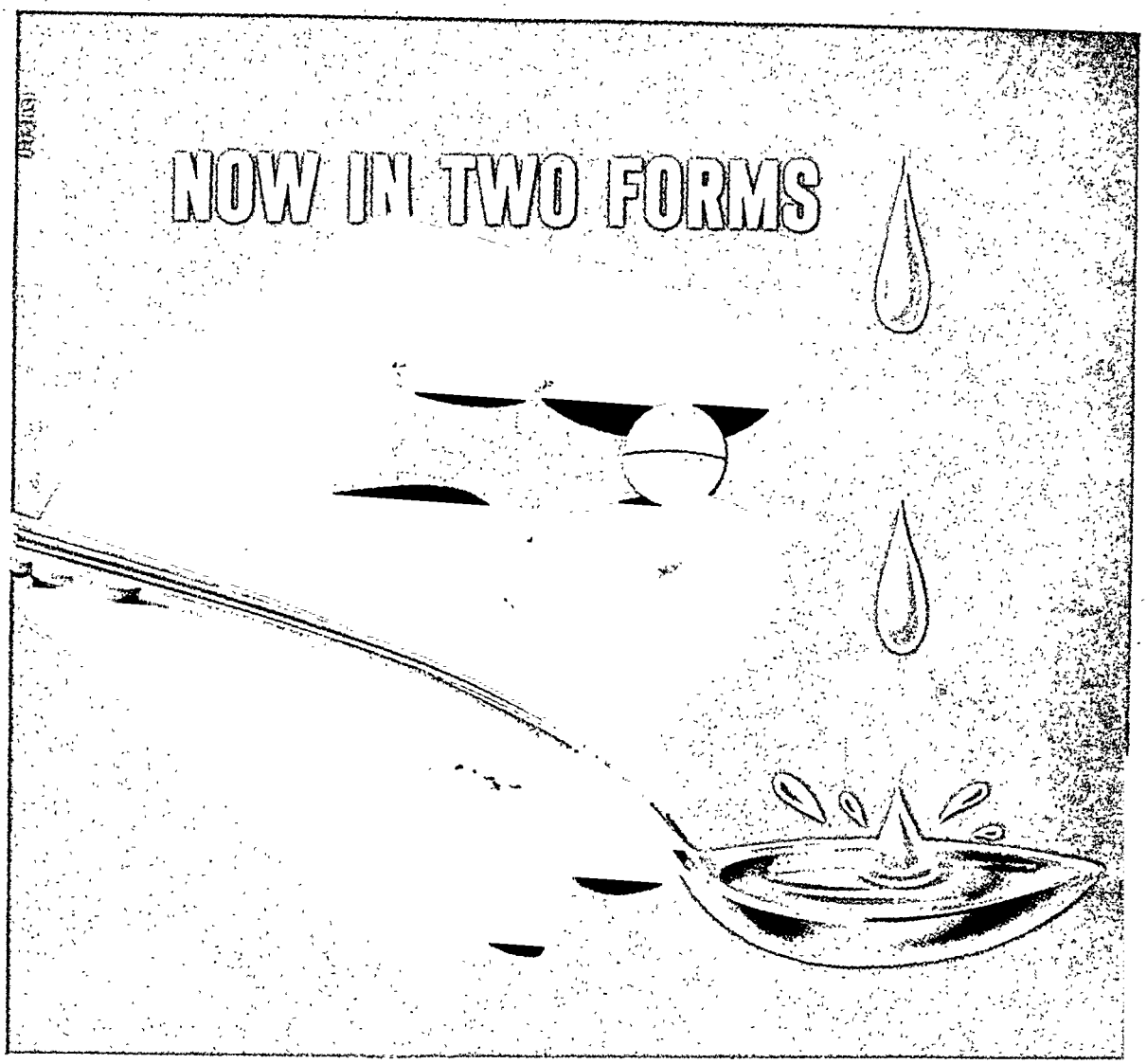
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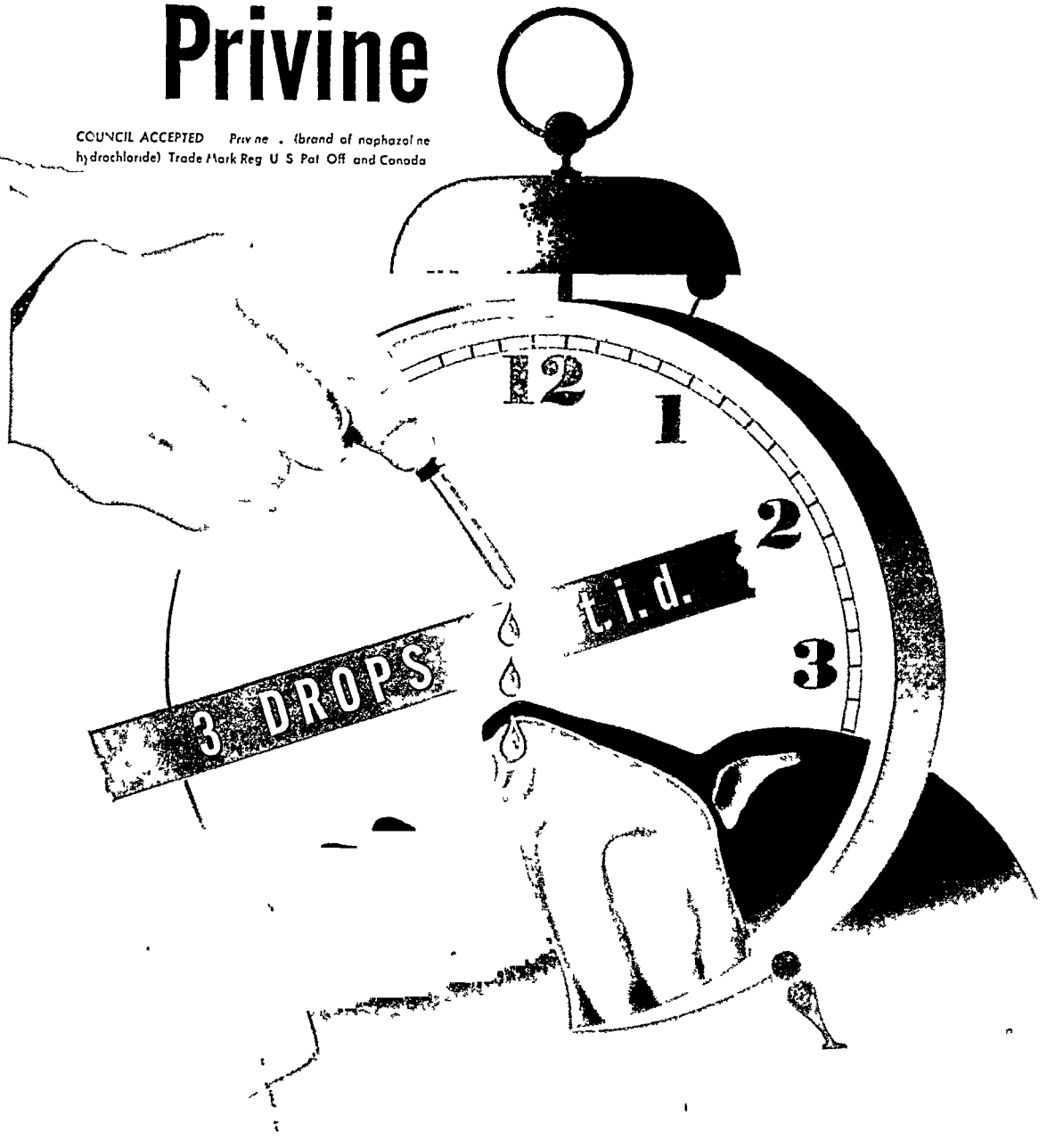
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In most cases, new drugs need a considerable period of trial before their true place and value are determined. A number of drugs have recently been made available for treatment of certain allergic conditions which are frequently difficult to relieve. These are discussed critically and conservatively in this article.

The Newer Antihistaminic Drugs in the Treatment of Allergic States*

LOUIS TUFT, M.D.

PHILADELPHIA, PENNSYLVANIA

The most recent development in allergy is the use of various antihistaminic agents. These are being employed extensively, though not always wisely, in the treatment of allergic ills, each new "cure" being replaced in turn by its successor as soon as its shortcomings become evident. The present review proposes, therefore, to discuss the reasons for the development of this form of treatment as well as the basic principles involved and the indications for the use of these agents.

It long has been suspected that histamine was the substance which was released into the circulation during the course of either the anaphylactic reaction in the lower animal or the allergic reaction in the human and that it was responsible for the symptoms of these reactions. This assumption has been strengthened greatly by many recent investigations which have shown fairly definitely that histamine was responsible for these reactions. Granting this to be so, attempts then were made to prevent or counteract allergic reactions by some type of antihistaminic agent or drug. Thus far, four methods have been employed.

HISTAMINE INJECTION (DESENSITIZATION)

This method sought to increase the tolerance of the patient to histamine by injecting it in increasing dosage and at frequent intervals. It was the earliest method tried, having been used as early as 1924 by Ramirez and St. George.[1] They injected histamine subcutaneously into ten patients with asthma but reported good results in only two. Indifferent results were reported by others in the treatment of asthma, hay fever, urticaria and migraine, so that the treatment temporarily was abandoned. With more favorable reports of its effects, its use was revived recently so that it soon was being used extensively in all types of allergy. Sufficient data have now accumulated that one should be able to appraise its clinical value satisfactorily. Unfortunately, this is not easy because appraisal depends often on personal experience and interpretation. Furthermore, when histamine is employed, it often is not the sole agent or method being used in treatment so that satisfactory controls are not always available. As nearly as one can judge from clinical experience and review of the literature, it would seem that histamine injection therapy is most helpful in urticaria and angioneurotic edema, in physical allergies affecting either the skin or nose and in some patients with allergic or migraine headaches, or with Ménière's disease. It apparently is ineffective in all other allergic conditions despite some enthusiastic reports of its value in hay fever, asthma or atopic dermatitis.

Dosage and Administration. Histamine usually is given subcutaneously but also may be injected intravenously in urticaria, migraine or Ménière's disease. It also is given occasionally by iontophoresis but this is not as practical. The dose varies with the condition for which it is given and the method of administration. It usually is prescribed in terms of histamine base in doses from 0.01 mg. to 1 mg. at intervals varying from twice a day to once every two to four weeks. It is available commercially in the form of histamine acid phosphate. This comes in ampoules or vials of a 1:1,000 solution containing 2.75 mg. of the histamine acid phosphate per cc. which corresponds to 1 mg. of histamine base. From this solution, dilutions such as 1:10,000 or 1:100,000 may be prepared for use in patients who cannot tolerate large initial doses without reaction. When given subcutaneously, the initial dosage therefore may be as low as 0.001 mg. (0.1 cc. of 1:100,000 solution) or as high as 0.1 mg. (0.1 cc. of 1:1,000 solution used undiluted). When given intravenously the preparation is diluted with normal saline in amounts varying from 10 cc. to 500 cc. depending upon the condition for which it is given. It is administered very slowly to prevent untoward reaction.

Reactions. When given subcutaneously and in small dosage, histamine usually provokes only slight and temporary local reaction. As the dosage increases,

* From the allergy clinic of Temple University Hospital and Medical School, Philadelphia, Pa.

Read before the Postgraduate Institute of the Philadelphia County Medical Society, April 18, 1947.

this local reaction becomes larger and constitutional signs appear. The most prominent is a rapid flushing of the face which appears within a few minutes after injection. When the reaction is mild, it disappears within 15 to 20 minutes. Severe reactions are more prolonged and may be accompanied or followed by flushing of the entire skin, chilliness, a choking sensation or dyspnea, syncope, rapid pulse and fall in blood pressure. These are symptoms of histamine shock and may require the administration of epinephrine for relief. Larger doses may provoke in some patients not only shock symptoms but headache and anginal pain; hence it either should be omitted entirely in older patients or those with cardiovascular disease or given with great caution and in small doses. The symptoms of histamine reaction appear more rapidly after intravenous injection, hence the necessity for the dilution of the histamine and its slow administration.

Mechanism. The mechanism by which the favorable effect of histamine therapy is produced, is not clearly understood; it apparently is not effective in those allergies where a specific antigen-antibody is demonstrable as in hay fever or allergic asthma. It is beneficial, on the other hand, in conditions like urticaria or physical allergy in which circulating antibodies and positive skin reactions regularly are absent. Histamine itself is not an antigen and does not induce antibody formation; hence its injection apparently does not act as a means of specific desensitization. From the evidence at hand, one can only conclude that histamine brings about its beneficial effect by increasing the tolerance of the patient's tissues to histamine released during the course of the allergic reaction. Alexander [2] has suggested that histamine given at frequent intervals induces a state of refractoriness probably lasting less than 48 hours; hence the beneficial effect of repeated doses at short intervals. This may be the true explanation of its action but it needs further confirmation. One thing is definite: histamine injections given to improve tolerance certainly do not represent the best approach in the treatment of allergic conditions; otherwise it would be unnecessary to have developed other methods of antihistamine therapy.

HISTAMINASE

In 1930 Best and McHenry demonstrated the presence of a specific enzyme designated histaminase in the intestinal mucosa which rendered histamine inactive within a few hours when combined with it in vitro. Subsequent experiments seemed to indicate that some inactivation also took place in the intact experimental animal. These facts stimulated the hope that since histamine presumably was the major factor in the allergic reaction, its action could be neutralized by the administration of histaminase. The latter therefore appeared to be an ideal therapeutic agent for human allergic disease, especially since it was nontoxic even in large amounts. It was introduced into clinical use in this country in 1938 and received extensive trial in various allergic disorders. Probably the earliest report was that of Foshay and Hagenbusch [3] who reported quite favorably on its use both orally and parenterally in the control or prevention of serum sickness.

Following this, an extensive literature has accumulated with conflicting reports as to its clinical efficacy, the reports often being dependent upon the enthusiasm of the author. It seems well established, however, that as with histamine, it is of no value in conditions like hay fever, allergic rhinitis, asthma or atopic dermatitis in which an immunologic mechanism is operative. The most favorable early results were reported in urticaria, serum and drug allergy and physical allergy. Recent reports have even doubted its value in those conditions, although it still is being employed by some. Even this limited application has been restricted or displaced by the use of other histamine antagonists. Probably the finishing blow to its clinical use was supplied by the statement of Best and McHenry [4] that after a period of ten years' investigation with this agent, they "believed there was no physiological basis to warrant its clinical use."

Administration and Dosage. Histaminase obtained by extraction from small intestines and desiccated kidneys of hogs, is marketed in the form of five-unit enteric-coated tablets designated as torantil. It is standardized biologically in histamine detoxicating units, each unit representing the amount which inactivates one milligram of histamine hydrochloride during incubation at 37.5° C. for 24 hours. It is important that the material should be biologically active, since some of the reported unfavorable results were attributed to the use of inactive material. It is not toxic and usually causes no untoward symptoms in the average patient. However, abdominal cramps from large doses have been noted in individuals and patients allergic to pork may develop gastro-intestinal symptoms because of the contained hog protein. The initial dose recommended was 10 to 15 units (two to three tablets) three times daily before meals. This would be increased to 20 or 25 in severe cases or decreased to a maintenance dose of 10 to 20 units daily after control of clinical symptoms. Histaminase also was marketed formerly in the form of 1.0 cc. ampoules, each containing one unit of the dry powder dissolved just before use in 5 cc. normal saline. This was given

intramuscularly twice a day along with the oral administration. It was used especially in serum sickness, either for actual treatment or prevention. Because severe untoward reactions were reported from the use of that preparation, it is no longer marketed.

HISTAMINE CONJUGATES (HAPAMINE)

Since histamine itself is not antigenic, it is detoxified quickly in the body and may induce unpleasant systemic reaction; it therefore does not lend itself readily to desensitization treatment. The use of histaminase as a neutralizer of histamine likewise failed to solve this problem. It was believed that the answer might be found by combining or conjugating histamine with a suitable protein to produce a compound which would stimulate specific neutralizing antibodies against histamine. This thought was based on the fundamental observations of Landsteiner showing that when simple chemicals are deazotized and coupled with a protein, the specificity of the resultant compound is determined by the hapten or simple chemical portion of the new molecule. It was hoped, therefore, that this might be true of histamine, which was a small, easily dialyzable, nonantigenic molecule. Accordingly Fell and his associates [5] in 1941 reported the successful preparation of a histamine azoprotein, called hapamine. This was synthesized by conjugating histamine with horse globulin from which the specificity had largely been removed. Experiments in lower animals showed that injections of this compound apparently induced the formation of large amounts of specific antibodies which neutralized or inactivated histamine and rendered the animal insusceptible to the action of histamine. These observations indicated that hapamine possibly might be helpful in the treatment of allergic disorders and seemed to warrant its clinical use.

Dosage and Administration. Hapamine is marketed in a 5cc. ampoule containing a 3 per cent solution preserved with phenol. It is standardized so that each cubic centimeter of the solution represents about 1 mg. of histamine. It apparently contains no free histamine nor is any appreciable amount liberated after its ingestion.

Hapamine is given by subcutaneous injection, starting with a small initial dose of 0.01 cc. If no reaction follows, increases of 0.01 or 0.02 cc. may be made at four- to five-day intervals until 0.1 cc. is reached. Dosage may then be increased more rapidly by 0.1 or 0.2 cc. until either symptomatic relief occurs or until 1.0 cc. is being given, provided there is no reaction. If the latter does occur at any level, the dose either should be reduced or omitted and a smaller dose given at the time of the next injection. When improvement takes place the interval may be prolonged to a week or longer. A more intensive dosage schedule consisting of the initial administration of 0.1 cc. followed by 0.5 cc. and a maintenance dose of 1.0 cc. at five-day intervals over a 30-day period is advocated by Cohen.[6] This course is repeated after a rest period of two months. For the administration of the smaller dosage, the hapamine solution may be diluted with sterile distilled water to make a 1:10 dilution. Each tenth of a cc. of this dilution will then represent 0.01 cc. of hapamine.

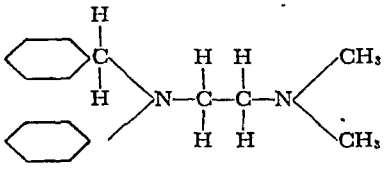
Reactions. Local and systemic reactions sometimes follow the injection of hapamine. These have been severe enough in some patients to constitute a definite disadvantage to the administration of this agent. The local reaction is mildly inflammatory in character with redness and swelling at the site of injection lasting from three to seven days. In some instances, small pea-sized nodules may persist for several months. Systemic symptoms reported as part of the constitutional reaction are urticaria, angioneurotic edema, dyspnea, wheezing, glandular enlargement, fever, abdominal cramps and on one occasion, exfoliative dermatitis. These symptoms may come on within a short time after the injection or may not appear until several days later. They are similar to those seen in patients developing serum sickness after horse serum administration. Since hapamine does contain a small amount of horse serum globulin it is not unlikely, despite its despeciation, that the mechanism of the reactions to hapamine is similar to that of allergy to foreign sera. This resemblance is emphasized by the appearance of reactions to hapamine following its re-injection after a free interval.

Clinical Value. Hapamine has been used extensively since its introduction in 1941 in all varieties of allergic disease including urticaria, angioneurotic edema, physical allergy (due to heat, light and cold), contact and atopic dermatitis, allergic rhinitis, hay fever, asthma and migraine. Conflicting opinions prevail in the reports. It was believed at first that the best results from this therapy were obtained in patients with skin or physical allergy and possibly in some patients with nasal or bronchial allergies provoked by such physical changes as exposure to cold. Thus favorable results were reported at first in patients with urticaria and angioneurotic edema, in some patients with contact dermatitis and in a few asthmatics whose symptoms followed exposure to cold. Subsequent clinical experience as indicated by the reports of others has failed to corroborate these results and even the slight benefit obtained by some patients has been attributed to the nonspecific effect of the agent rather than to any antihistamine effect.

The possibility of discomforting systemic reaction likewise has detracted from its more extensive clinical use. While it still is being used by some in allergy treatment, it apparently has only a limited clinical application, possibly in patients in whom other measures fail. It certainly cannot be considered the ideal answer to the problem of antihistamine treatment.

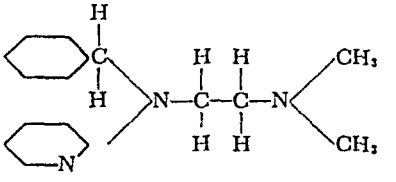
HISTAMINE ANTAGONISTS (ANTIHISTAMINE DRUGS)

Attempts have been made for years to prevent the phenomenon of animal anaphylaxis with all kinds of chemicals, drugs, and biologic agents in the hope that they likewise would be useful in the human. These efforts usually failed, either because of the ineffectiveness or impracticability of the agents or their toxicity. With the demonstration of the importance of histamine in the allergic reaction and particularly with the apparent failure thus far to produce satisfactory results with histamine desensitization or conjugation, attention again is being directed to the development of drugs which can successfully neutralize or inactivate histamine. Several have been synthesized recently and offer some hope of being helpful in the treatment of allergic disorders. The first of the newer group of compounds investigated were amino acids, including histidine, cysteine and arginine. While these brought about some inhibition of anaphylaxis and histamine activity in the lower animal, they were too toxic for clinical use and clinically ineffective in nontoxic dosage. A more favorable approach to this problem was offered by the development in France by Fourneau and his co-workers, of certain phenolic ethers of amino alcohols which were definitely antihistaminic in action. At first these compounds were found to be too toxic to be useful clinically. However, in 1942, Halpern [7] and others reported good clinical results with compounds similar to that originally developed by Fourneau. One of these was known as 2339 R P and sold commercially as Antergan. It was found to possess adequate antihistamine qualities and was sufficiently nontoxic to warrant its clinical use. Limited clinical trial by French physicians indicated possible effectiveness in patients with skin or nasal allergies and in some patients with serum sickness, asthma or migraine.



ANTERGAN

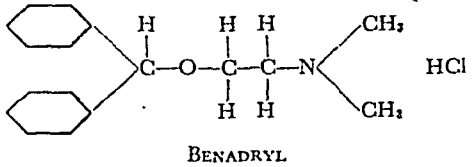
During this period American research workers likewise have been experimenting with antihistaminic compounds, two of which proved effective enough to warrant extensive clinical trial. The first one, developed by Mayer and his associates,[8] is known commercially as Pyribenzamine or P.B.Z. It is a pyridine derivation of the general formula. A glance at its chemical structure shows that it resembles that of the



PYRIBENZAMINE

French preparation Antergan. Experiments in lower animals showed it to be even more antagonistic to the action of histamine than Antergan and nontoxic in character.

The second of these antihistaminic compounds is Benadryl. This is a benzhydryl alkamine ether first



BENADRYL

introduced and studied in 1945 by Loewe and his associates.[9] They found it to be effective experimentally in histamine and anaphylactic shock in the lower animal and like Pyribenzamine nontoxic in character. Both these drugs now are being given an extensive clinical trial and numerous reports as to their value already have been made.

Dosage and Administration. Pyribenzamine is a stable, readily soluble white crystalline material. It is put up in 50 mg. scored tablets so that they can be broken in half when a smaller unit is needed. The dosage varies from 50 mg. daily to as high as 600 mg. It is best to begin treatment in adults with a 50 mg. tablet four times daily after meals to see whether the patient can tolerate the drug or not. If not, the dose can be reduced accordingly. If the patient has no untoward effects from its ingestion but the symptoms are not controlled, the dose should be increased to two tablets four times daily or even to three tablets at a dose if symptoms are unrelieved and side-effects absent. When symptoms have been relieved adequately, the dosage may be reduced to 50 mg. or less and gradually withdrawn. The dosage in children is proportionate to their age and weight. In general it should be about one-half the adult dose.

Benadryl is put out in the form of 25 and 50 mg.

capsules and an elixir containing 10 mg. per dram. The dosage for the capsules is similar to that of Pyribenzamine in adults. If this is not well tolerated, even in small amounts, one can then use the elixir so as to readily provide doses of only 10 mg. This latter preparation is advantageous for administration to children where smaller dosage is desirable.

Reactions. The great disadvantage of both these drugs is their side-effects. These never are serious but sometimes are sufficiently discomforting to necessitate withdrawal. Many patients will develop minor but tolerable symptoms from the drugs; at times these symptoms will lessen or disappear when the drug administration is continued. The most frequent and important side-effect is drowsiness, which seems more frequent from Benadryl than from P.B.Z. In fact, this may be so extreme, from even one dose, that the patient may remain sleepy for a number of hours afterward. It is best to warn patients about this possible symptom. At times this drowsiness may be counteracted by the use of caffeine or strong coffee. However, if this fails, it may become necessary to withdraw the drug completely.

In addition to somnolence, other untoward symptoms which have been reported include headache, vertigo, confusion (at times amounting to irrationality), dryness of the nose and mouth, nausea, abdominal discomfort, weakness, nervousness and palpitation. These are less severe than the drowsiness and less often require withdrawal of the drug. What effect, if any, the continued ingestion of these drugs over long periods of time will have on the nervous systems and especially on the hematopoietic systems (in view of the presence of benzene rings) remains for future investigation to demonstrate.

Clinical Value. It still is too early to properly evaluate the clinical effects of these drugs. They are now being employed in nearly all varieties of allergic disorders regardless of whether their use appears to be indicated or not. From the evidence at hand now, it seems that they, like other antihistaminic remedies, find their greatest sphere of usefulness in the urticarial group of conditions, in hay fever, in some patients with migraine, Ménière's disease, allergic headache and in serum, drug or physical allergy. They seem to be less beneficial in asthma, allergic rhinitis, and contact and atopic dermatitis. Future clinical experience with these drugs no doubt will more clearly define their indications and contraindications. It must be emphasized, however, that they are not curative—offering symptomatic relief only. In most instances, the withdrawal of the drug is followed by recurrence of symptoms unless in the meantime the offending agent has been discovered and eliminated.

CONCLUSIONS

Four methods have been employed within recent years to counteract the effect of histamine, considered to be the cause of allergic reactions. Of these histamine by injection is of some value in a limited number of allergic conditions, notably the urticarial, physical and headache groups, although its effect is not that of true desensitization and often is temporary. Histaminase, the histamine-inactivating enzyme, and hapamine, a histamine conjugate, both have failed to be helpful clinically and are being rapidly discarded. The newer antihistaminic drugs, notably Benadryl and Pyribenzamine in the United States, and Antergan and related French compounds abroad, seem to be quite beneficial in symptomatic treatment of urticaria, angioneurotic edema and allied disorders, serum, drug and physical allergies, certain types of allergic and migraine headaches and in seasonal hay fever and pollen asthma. They have proved disappointing in nonseasonal asthma, allergic rhinitis, and allergic dermatitis of the atopic or contact variety. Furthermore, their use may be accompanied at times by unpleasant side-effects sufficient to necessitate their discontinuance. It also must be remembered that they are palliative but not curative in their therapeutic effect.

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Acute renal failure of the kind described in this article is occurring more frequently with the increased use of certain drugs and procedures and is of special medical importance. If the patient can be assisted over the acute attack, recovery is ordinarily complete and without sequela. Mortality is high, however, and only by a prompt diagnosis and a clear understanding of the principles of treatment can the greatest number possible be saved.

The Clinical and Therapeutic Aspects of Acute Renal Insufficiency Due to Lower Nephron or Hemoglobinuric Nephrosis*

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The relentless course of chronic Bright's disease terminating with death in uremia is well known. This report will be confined to a smaller group of cases with a characteristic anatomic lesion in which the kidneys prior to a sudden insult have been essentially normal, and in which abrupt renal failure follows this insult.

This presentation will include a discussion of the pathologic lesions encountered in such acute renal insufficiency, the most common etiologic factors, the biochemical and physiologic alterations resulting, the principles of treatment, and some therapeutic errors to be avoided.

PATHOGENESIS AND CLINICAL CHARACTERISTICS

The majority of instances of acute renal insufficiency in the author's experience have been those which, if death occurred, showed at necropsy a lower nephron (hemoglobinuric) nephrosis. This lesion has been described in detail by Mallory et al.[1] and Lucké.[2] Briefly it consists of pigment deposition in the distal renal tubular lumina, degenerative and later regenerative changes in the tubular epithelium in this area, interstitial inflammation, and practically no anatomic changes in the glomeruli.

The clinical conditions which can cause this anatomic lesion are numerous. The most important are: (1) severe or prolonged shock and trauma [1-4] including the crush syndrome; [1, 5] (2) massive intravascular hemolysis of donor erythrocytes following administration of incompatible blood; [6, 7] (3) intravascular hemolysis of the patients' erythrocytes following administration of distilled water intravenously and certain drugs,[7] following thermal burns,[8] in blackwater fever,[2, 9] and possibly rarely in paroxysmal and nocturnal hemoglobinurias; (4) sulfonamide reactions unaccompanied by manifest intravascular hemolysis [1, 2, 10] and (5) a miscellaneous group including hyperthermia and various poisons.[2] This list is by no means complete but includes the most frequent conditions capable of producing lower nephron nephrosis. Why such apparently unrelated pre-existing conditions terminate in this lesion is not entirely clear; some possibilities are mentioned in other reports.[1-4]

Whatever the initial insult the sequence of events is much the same in this syndrome. A typical case in which shock appeared to be the primary factor serves as an example:

An 18-year-old mountain infantryman sustained multiple wounds from enemy shell fragments.[1] En route to the field hospital he received 500 cc. of plasma. On arrival five hours later he was in severe shock. Eleven hours after wounding and receipt of 4,500 cc. of blood, the blood pressure was 105/60; he was successfully operated upon without the necessity of further transfusion. That afternoon his condition was quite good, but he had not yet voided. The following day he seemed better, and voided 300 cc. of urine. Three days after wounding he was mentally clear, but appeared slightly edematous. The blood pressure was now 145/100. During the remaining three days of his life his urinary output varied between 100 and 500 cc. daily, the hypertension persisted, edema increased despite an oral intake of only a liter of fluid daily, his nonprotein nitrogen rose to 287 mg. per cent, and he died in uremia seven days

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after wounding. Postmortem examination revealed a lower nephron nephrosis.

In instances where the initial insult has been one of the other factors mentioned above, a similar pattern is followed clinically. After excessive intravascular hemolysis, crushing injury, sulfonamide administration, or a severe burn, anuria or oliguria develops. These are followed by a moderate hypertension, edema, unless fluid and electrolyte intake are scrupulously controlled, occasionally convulsions, and eye-ground changes consisting of hemorrhages and exudates in some instances. The general appearance of the patient, in our experience, may be quite good and belies the seriousness of the situation. The outcome is usually death in uremia or from pulmonary edema within ten days after the onset of renal failure. Occasionally evidence of improving kidney function, as demonstrated by diuresis, may occur at any time during the course with subsequent complete recovery. The signs of returning function may not appear, however, until the end of the second week. This time factor is of extreme importance from a therapeutic standpoint, and will be discussed further under the section on treatment.

Those cases clearly resulting from massive intravascular hemolysis deserve special mention. The renal failure following administration of incompatible blood resulting in agglutination and hemolysis of the donor erythrocytes, hemoglobinemia and hemoglobinuria is well known. *Fatal* renal insufficiency from hemolysis of the patient's erythrocytes such as occurs after receipt of distilled water intravenously; in acute hemolytic anemias, including those due to drugs; in paroxysmal or nocturnal hemoglobinuria; or, in blackwater fever is less common. Recent studies have emphasized the importance of such intravascular hemolysis resulting from absorption of distilled water during transurethral resection of the prostate.[11, 12]

Sulfonamide sensitivity probably accounts for a considerable proportion of the cases encountered clinically which show lower nephron nephrosis at autopsy. The pathogenesis here is even less clear than in the patients in whom there has clearly been intravascular hemolysis, shock or both. Renal failure may occur after a small, single dose of the drug, and is apparently explained by a sensitivity of the renal parenchyma to this chemotherapeutic agent. It is not necessarily associated with an acute hemolytic anemia. Indeed, in our experience evidence of any extensive intravascular hemolysis has usually been lacking, though existence of hemoglobinemia at some time during the course could not definitely be excluded.[1] The renal failure of this type should be sharply distinguished from the more common sulfonamide lithiasis in which sulfonamide precipitation occurs in the ureters or calyces and in which it is usually possible to remove the precipitated sulfonamide mechanically by cystoscopy and by ureteral and pelvic lavage.[13, 14]

The course of renal failure due to the crush syndrome is little different from that described above. There is good evidence that the primary agent responsible for the kidney damage may be myoglobin released into the blood stream from the injured muscles and excreted by the kidneys soon after removal from the crushing influence.[1, 5, 15] Similarly, the course of the patient whose renal function fails after severe burns follows a course of progressively developing uremia until death or recovery diuresis supervenes.[8] Reports in the literature of kidney failure in blackwater fever during malaria indicate that the clinical course is identical with that described here.[2, 9]

DIFFERENTIAL DIAGNOSIS

That mercury can cause destruction of the renal tubules, both proximal and convoluted, and result in death from uremia is well recognized.[16] Acute bilateral cortical necrosis rarely is the cause of sudden renal failure which remains unexplained until autopsy is performed. Although usually associated with pregnancy, it has been observed in males and in all age groups.[17] Periarteritis nodosa may cause unexplained acute renal failure, and must be considered in the differential diagnosis. The onset and early course of acute glomerulonephritis are not like that of this syndrome, and should rarely offer difficulty in differentiation.

Chronic but essentially latent Bright's disease, subjected to the strain of acute illness, anesthesia and operation, or trauma with resultant acute renal failure, may be difficult to differentiate from the lesion under discussion, and indeed the former may be superimposed upon the latter. The history and previous laboratory determinations of the urine, if known, are of help, but definite exclusion of underlying renal disease may be impossible until later. During the acute emergency this differentiation is of little practical moment for the therapeutic principles to be followed are the same. If the patient survives the acute crisis, subsequent observation should allow the physician to decide upon this important issue. In our experience complete recovery from lower nephron nephrosis, uncomplicated by pre-existing kidney disease, is the rule if the patient lives through the first critical days or weeks.

BIOCHEMICAL AND PHYSIOLOGIC ALTERATIONS OF THE BLOOD AND URINE

Whatever the pathogenesis, once renal failure has developed the physiologic and biochemical consequences are similar. Those seen in this syndrome have been described in detail in separate reports.[1, 4] Mention will be made here of them chiefly as they are of therapeutic importance. The expected azotemia, and hyperphosphatemia (accompanied by hypocalcemia) develop rapidly and progressively. There is usually a mild acidosis as reflected by lowered carbon dioxide combining power of the plasma. Plasma chlorides vary from hyperchloremic to hypochloremic levels but as a rule are low, possibly related in part at least to plasma volume changes discussed below.

The specific gravity of the urine rapidly becomes approximately that of the glomerular filtrate. In cases in which recovery occurs, ability of the kidneys to excrete a concentrated urine is one of the last functions to return to normal. Phenolsulfonephthalein excretory capacity is markedly diminished. In a limited number of cases where the measurements were made, glomerular filtration rate (mannitol), effective renal blood flow, and maximal tubular excretary capacity for sodium para-aminohippurate were all diminished in approximately the same proportions, and where recovery occurred these components returned toward normal at about the same rate.[1, 18]

Of great therapeutic importance is the fact that most such cases develop marked increases in plasma volume even in the absence of demonstrable clinical edema. This increase seems to be largely related to a discrepancy between fluid output and fluid intake, and is a reflection of the usual therapeutic error of too enthusiastic administration of water and electrolytes. Thus in 19 fatal cases studied, which showed a characteristic lower nephron nephrosis at autopsy, the average plasma volume was increased 41.6 per cent ± 6.6. In 15 of these which received over a liter of crystalloid or colloid solution intravenously daily, the average increase was 46.9 per cent ± 6.6, while in four cases which received less than a liter daily the average increase was 21.8 per cent. In three cases in which recovery occurred, and in which it was possible to make serial measurements, it was observed that the time of maximum plasma volume increase coincided with the time of greatest nitrogen retention, and that as the retained nitrogen was cleared the plasma volume returned to normal.[1, 4]

If attempts have been made to produce an alkaline urine by the administration of large amounts of alkalies, the electrolyte structure is likely to be that of a severe alkalosis complicating the renal failure. The excess of sodium likewise enhances the plasma volume increase. In spite of a dangerous metabolic alkalosis, an alkaline urine was produced only rarely in our experience.[1, 19]

TREATMENT

Primary treatment should be directed towards prevention of those factors known to be of importance in the production of lower nephron nephrosis. There is good evidence that a shock-like state with accompanying renal ischemia may have occurred at some time in most cases.[1-4] Prompt and adequate resuscitation of every patient in shock is then of great importance. Rigid checking of donor compatibility in every patient to be transfused and distinctive labelling of bottles containing distilled water could completely eliminate intravascular hemolysis from these causes. Prevention of those cases due to sulfonamide sensitivity is more difficult because anuria may follow administration of a single small dose of the drug.

Once the syndrome has developed treatment is disappointing, and mortality is high whatever course is followed. Since a few cases do recover spontaneously, and since in our experience there are no positive measures capable surely of re-establishing renal function, the aim should be one of tiding the body over the period of the first critical days until such time as the kidneys may again begin adequately to excrete urine. The principles to be followed in realizing such an aim, and in avoiding the errors which may produce a fatal outcome, will be presented.

Evidence has been cited that in this syndrome, and probably in acute renal insufficiency from any cause, plasma volume is elevated even where fluid intake appears not to be excessive. It is not surprising that with the former practice of giving large quantities of fluids containing sodium and chloride parenterally, most such patients have died of acute pulmonary edema. Once deficient blood volume has been replaced and hydration affected, and unless extrarenal water losses are great, the total water requirement of the average patient with oliguria or anuria does not exceed 500 to 1,000 cc. daily. The total intake should not exceed this quantity until there is evidence that the kidneys will respond to a larger intake by excreting a greater volume of urine. Oral fluids are preferable where possible and such parenteral fluids as are used should be administered slowly.

Because of the water-retaining properties of sodium, salt solutions should be used with precaution and for

specific needs only. These needs may be difficult to estimate. In our experience, 300 cc. of physiologic saline daily (approximately 2.5 Gm. of sodium chloride) fulfill the maximum requirements during the anuric or oliguric periods unless there is excessive electrolyte loss from sweating, vomiting or diarrhea. The advisability of giving hypertonic solutions parenterally is highly debatable. From our extensive use of them in various forms they appear to have little effect upon the output of urine and they may dangerously increase plasma volume.[1, 4]

The known diuretic effect of alcohol and the suggestion that it might increase renal blood flow [20] prompted a trial of this agent in 20 patients who died primarily of renal insufficiency. In a few of them a transient increase in urinary output occurred, but similar increases were found in those who received no alcohol. Mercurial and xanthine diuretics, magnesium, potassium and sulfate salts were without beneficial effect in our hands. Spinal anesthesia in two patients, and kidney decapsulation with sympathectomy in one did not alter the fatal outcome.

Ideally, nutritive requirements during the acute phase should be met by an adequate caloric intake, but with such foods that there is minimal destruction of body protein and production of urea nitrogen from exogenous proteins. These demands would best be served by a carbohydrate and fat intake sufficient to furnish 1,500 to 2,000 calories per day. If the patient is unable to take food by mouth it is practically impossible to administer enough glucose intravenously to furnish such a caloric intake and still adhere to the more important rules of restricting fluids and prohibiting hypertonic solutions. During the acute phase of renal insufficiency one must be content with merely furnishing the small requirement of sodium chloride as physiologic saline and with an attempt to meet caloric requirements by supplying glucose in a 5 per cent solution in water in the additional small fluid allowance remaining—that is, a total daily intake of 500 cc. to 1,000 cc.

In the treatment of this syndrome, alkalies have been recommended to relieve acidosis and to produce an alkaline urine in order to make more soluble abnormal blood or muscle pigments and sulfonamides as they are excreted in the urine. Evidence has been presented that once renal insufficiency of the type described in this report becomes established it is practically impossible to produce an alkaline urine. A dangerous metabolic alkalosis may be produced in the attempt. The use of alkalies in one patient we observed was almost surely at least partially responsible for his subsequent death from renal insufficiency.[1, 19] There is some evidence in the literature that alkalies in large doses per se, may cause lower nephron nephrosis.[2, 21]

If any doubt exists as to the presence of sulfonamide lithiasis, cystoscopy and ureteral lavage are clearly indicated as soon as renal failure manifests itself.

Measures designed to remove nitrogenous and other waste products from the blood by dialysis merit consideration. Indeed it would seem that if such methods could be perfected they would have the widest field of usefulness in this syndrome, for with it we know the kidney is capable of repairing itself. Peritoneal lavage has chiefly been employed in this country with some degree of success.[22] The greatest hazard with it has been the occurrence of peritonitis in a high proportion of cases despite liberal use of antibiotics. In three cases in which this method has been observed by the author, a second and equally troublesome factor has been that of controlling water and electrolyte balance despite the theoretical possibility of doing so by varying the electrolyte structure and osmotic pressure of the lavage fluid.[23] Kolff in Holland has recently described an "artificial kidney" by which arterial blood passing through cellophane tubing is almost completely cleared of urea during dialysis.[24] He has encountered no infection during the use of his method, a distinct advantage over peritoneal lavage. A serious objection is that 500 to 750 cc. of blood are in the dialyzer at one time.[25] As a result varying degrees of shock would seem inevitable, clearly an undesirable effect in a condition where shock so frequently plays an important role in pathogenesis. Any such method should be reserved only for those patients in whom the outlook is clearly hopeless. Definition of such a patient is very difficult, for diuresis may set in as late as ten days or more after onset of the renal insufficiency.

SUMMARY

1. Acute renal insufficiency due to lower nephron nephrosis may follow several clinical conditions. The most important of these are intravascular hemolysis, prolonged shock and trauma, sulfonamide sensitivity, thermal burns and blackwater fever.

2. Whatever the precipitating factor the clinical sequence of events and the physiologic alterations resulting are similar and are those of renal insufficiency. Increase in plasma volume has regularly occurred in the cases we have studied.

3. No positive measures capable of surely re-establishing renal function have been observed. The aim in therapy therefore should be one of tiding the body

over until such time as kidney function may become re-established.

4. Mortality is high whatever therapeutic course is followed, but avoiding the usual practice of forcing fluids in such patients should reduce the high incidence of death from pulmonary edema and provide a few with the chance of spontaneous recovery of renal function.

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To the physician caring for industrial workers, and especially to the novice in the field, this paper will be very helpful. The important features in the recognition and prevention of industrial dermatitis are clearly set forth.

Industrial Dermatitis*

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Industrial dermatitis presents a challenging problem. Skin diseases arising in the course of industry cause considerable disability. While admittedly mostly of a partial and temporary nature, this disability is nevertheless often complete and in rare instances even permanent. It is generally recognized that most cases of industrial dermatitis are preventable. Yet year after year thousands of dollars are lost in wages and equally large sums are paid out in compensation and medical care.

There is a great need for a better understanding of this problem. Working men need instruction in the hazards of their work. Foremen must be alert and on the lookout to detect early cases and to enforce compliance with standardized manufacturing procedures. Safety engineers must work with physicians to isolate offending materials and devise methods for the elimination of hazards. The value of the industrial nurse in preventive management must be more generally recognized.

The purpose of this paper is to engender a better comprehension of industrial dermatitis. Time does not permit discussion of the dermatologic problems incident to individual industries. Suffice it to say there is scarcely a single occupation which does not present some hazards to the skin. Bakers, building cleaners, maintenance men, cement workers, chemical workers, dishwashers, dye workers, electroplaters, gardeners, machinists, painters, photographers, tanners, and "soda jerks" are but a few of the groups exposed to high cutaneous hazards. Acids, alkalies, dust, paints, dyes, woods, metals, rubber compounds, petroleum products, and various solvents are agents which frequently irritate the skin.

The industry which concerns the production, processing, and preservation of food may be used as a representative example. Random sampling in this field recalls the "red feed" poisoning of fishermen, milker's eczema of dairymen, erysipeloid of butchers, ragweed sensitivity in farmers, and the "grocer's itch" in those who handle dried fruits. The picking and packing of fresh fruits, especially citrus fruits, produces skin irritations in those who are sensitive. Bakers may be allergic to the bleaches used in flour or even to the flour itself. A recent patient who was a baker had a vesicular eruption of the hands. He was found to be sensitive to wheat, barley, and rye. Cheesemakers may get an itch from small mites which infest the cheese. Some of these dermatoses are oddities, and prompted much investigation before their final elucidation. Among these is the erosion of the fingernails which occurs in those slaughterhouse workers who handle the sweetbreads. The digestive action of enzymes is responsible. The so-called "hog itch" of meat packers is due to a sensitization to the secretions of parasitic round worms which inhabit the intestines of the slaughtered hogs. Several papers have been written on the dermatologic problems of the food industry alone. This brief résumé merely serves to demonstrate the extent of the problem in a single industry.

It is estimated that ten to twelve per cent of all skin diseases are industrial in origin. This figure varies with the location of the physician, but it is an accepted average for the United States. Occupational dermatitis accounts for approximately 65 per cent of all industrial diseases excluding accidents. Hence, the importance of the subject is obvious. It is conservatively estimated that there are about 50,000 cases of industrial dermatitis each year in the United States.

There are many factors which predispose to industrial dermatitis. The worker's race has a known influence. Negroes and dark-skinned individuals are less sensitive to irritants than fair-skinned workers. Perspiration is also a factor. The more one sweats, the more dirt is held in the perspiration, and the more the worker rubs his face with his hands. Very dry

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An address delivered before the Wisconsin River Valley Safety Conference, June 5, 1947.

skins and excessively oily skins are also liabilities. Diet may influence susceptibility, and the worker's age must also be considered as a factor. As a rule, young untrained workers are more prone to enter hazardous industries, and their lack of experience leads to carelessness in handling irritants. On the other hand, dermatitis in the aged is notoriously stubborn in its response to therapy. The sex incidence is about equal, notwithstanding the fact that women are generally conceded better habits of cleanliness and are not employed in obviously dangerous occupations. The season of the year also exerts an influence. In summer less clothing permits more exposure. In winter there is less bathing, and comfortable working clothes being changed less frequently are permitted to become saturated with irritants. Other skin diseases which the worker may have, especially itchy ones, may predispose to further injury. Itching, with subsequent scratching by contaminated hands allows more exposure. During pre-employment physical examinations all workers with eczema may justifiably be excluded from industries with a known high incidence of dermatitis. The worker's personal and familial allergic history is also to be considered. Those of highly allergic stock with histories of various hypersensitivities such as asthma, hayfever, and eczema are poor candidates for employment in certain occupations. And lastly it should be mentioned that poor hygiene and lack of cleanliness are probably the foremost of all predisposing causes.

There are two great divisions of industrial irritants, the primary irritants and the sensitizers. A primary irritant is a substance which in ordinary working concentrations irritates all skins. Strong acids, alkalies, metallic salts, heat and cold, and certain solvents belong in this class. Thus, any worker putting his hands into sulfuric acid may expect to receive a serious injury. A primary irritant is harmful to everyone. On the other hand, the sensitizers are substances which in ordinary concentrations are harmless. Everyone may handle them without ill effects to begin with. However, through repeated exposure a sensitization or allergy is developed in some of the workers. Thereafter further contact with this substance by them is no longer without danger. Almost all chemical substances are potential sensitizers. Dyes, formaldehyde, lacquers, turpentine, chromium compounds, nickel, resins, and munitions are frequent offenders in this class. The same substance in different concentrations may be either a primary irritant or a sensitizer.

The length of time between the initial exposure and the onset of sensitization varies greatly. One worker may become sensitized in two weeks. Another, working with the same substances, may not become sensitized for ten years. This little-understood point often prompts the question, "How can I be sensitive to something in my work when I've done the same job for years?" The cause of these belated sensitizations cannot always be fully explained. Illness and fatigue may play a role, but other factors are also suspected. Among these, local cutaneous injury is important. For example, a man may work for a long time with potential sensitizers without developing a dermatitis. Then one day his hand is burned on a hot machine. He continues on the job, but several weeks later the onset of a sensitization dermatitis at the site of injury is recognized. A sudden increase in exposure may also cause a breakdown of immunologic barriers. For example, a worker sorted and stacked glued veneer woods for several years without showing any skin irritation from the glue. Then he was transferred to work in the "glue room" where the various glues were made up and mixed. Here he was literally splattered with glue and in a short time he developed a severe dermatitis.

Once a worker becomes sensitized to one substance he may develop other sensitivities more easily. A worker may develop a dermatitis from a known substance in his work, recover, and be warned against reexposure. In several weeks he may return to the physician with a flare-up of his dermatitis. Detailed questioning discloses that he has not returned to his old job, has not worn his old work clothes, has not been visited by his cronies from the factory, etc. Retesting reveals that he has become sensitized to another substance which he apparently tolerated in the past without difficulty. This phenomenon is known as "synergy" and numerous examples are reported in the literature. It is a constant source of confusion to physicians to say nothing of the consternation it produces in the industrial commission which must decide at which point industry ceased to be responsible.

One other phenomenon should be mentioned. In exceptional cases, such as workers with tetryl, a sensitization dermatitis develops soon after the initial exposure. If the worker remains on the job he slowly develops an immunity and his dermatitis leaves. He may lose this immunity during lay-offs and over vacations. On his return to work he again breaks out, but again he ultimately becomes immune. This occurrence is known as "hardening," and it may be compared with recurrent seasickness which may affect the best of sailors for the first few days of every cruise. "Hardening" is a very pleasant surprise when it occurs,

but it is the exception rather than the rule. It should not be awaited except in those industries where it is recognized as commonplace and regarded more or less as an initiation formality. More frequently, a sensitization dermatitis, once it appears, continues to get worse until the worker is removed from his job.

The diagnosis of industrial dermatitis is sometimes easy, but more often it is difficult and requires experience and training on the part of the physician. When a worker amputates his finger in a machine, the injury is obvious and there is usually no question as to industrial responsibility. However, the picture is quite different with industrial dermatitis. Here the onset is often slow and insidious, and the beginning may be overlooked or even disregarded by the worker. The physician cannot be influenced simply by the patient's introductory statement, "I got this from my job." The cause remains to be proved, and in so doing the physician cannot show partiality. He is simply interested in forming a scientific, unbiased opinion.

In arriving at a diagnosis of industrial dermatitis the doctor relies upon several different sources for information. He first must question the patient closely regarding the history of his skin eruption. "When did it first appear, where did it first appear, what is his work, how long has he worked at that job, what are his hobbies, does he work in the garden at home, do other workers have similar eruptions, does it improve over week-ends and during vacations?" and so on. The more detailed and thorough the history the better, because often an inkling of industrial or nonindustrial origin is obtained from this source alone. Most patients are fair in relating the history of their illness. Skilled, high-wage workers are inclined to minimize the causative role of their work and, as a rule, are anxious to learn their job is not responsible. Transient, low-wage workers, on the other hand, may tend to over-incriminate their jobs. Some of the criteria used in determining the industrial status of a dermatitis are: (1) The eruption necessarily appeared sometime after exposure. (2) In general it first appeared and is more severe in areas of maximum exposure to the suspected irritants. (3) It clears up or improves after removal from contact and reappears again soon after a return to the same exposure. These criteria serve as guides, but it must be realized that exceptions are frequent.

Another valuable aid in diagnosis is the patch test. Suspected materials are placed in contact with the skin and held in position with adhesive tape for varying periods of time. The selection of materials for patch testing, the proper concentration of those materials, the application of the test, and the reading and interpretation require experience. In the past, patch testing has been abused, especially in pre-employment examinations. As a result of indiscriminate use, it has been condemned and criticized by some. The details of patch testing, its merits and pitfalls will not be discussed here. Suffice it to say, the patch test, when properly used and thoroughly understood, is a valuable diagnostic tool.

Of course, clinically the eruption must be of a type which is compatible with a diagnosis of industrial dermatitis. Of the many different skin diseases there are those which may or may not have an industrial background. On the other hand, many skin diseases are never considered to be of industrial origin. If on examination the physician diagnoses a skin disease of this latter category such as psoriasis or pityriasis rosea, he immediately discounts the claims of industrial etiology. Recently a worker who carries strips of a plastic material on his shoulder claimed that his skin rash resulted from plastic dust infiltrating down through his open collar. Examination of the base of the neck and shoulders disclosed typical lesions of tinea versicolor, a disease not considered to be of industrial origin. The clinical diagnosis was then verified by the microscopic demonstration of the causative organism. The patient was informed of his diagnosis and told that his work was not responsible. He then recalled having a similar eruption while stationed with the army in the South Pacific several years ago. Lists of occupational and nonoccupational skin diseases have been promulgated, and these are universally adhered to in rendering decisions except in the rarest of instances. The history must also agree with the type of lesions presented. A patient cannot claim that keloids or a chronic radiodermatitis resulted from a recently acquired job when it is well recognized that these lesions require months and years to develop.

The duration of industrial dermatitis varies greatly. Eruptions may recede within days or weeks, but they may persist for months or even years. In general, a nonsensitizing dermatitis is of shorter duration and averages about three weeks. A sensitizing dermatitis is a more persistent injury and on the average lasts about three months. Cases lasting three or four years, although rare, are not unheard of. As a rule, any case which persists over three months without exposure to the original contact substance warrants a review of the findings with hospitalization and further study of the patient. A papermill worker, while hospitalized here with a severe dermatitis, was shown to

have a chromate sensitivity. He also suffered from asthma. His dermatitis gradually cleared, and he returned to his old job against advice. He suffered a severe flare-up and was hospitalized a second time. On this admission his dermatitis was more extensive, and the response to treatment was more slow. However, after several weeks he was discharged improved, but disabling residuals of dermatitis persisted and prevented any work. The patient was then followed over a three-month period and no definite tendency toward healing was observed. At this time consultation elsewhere confirmed the original diagnosis of industrial dermatitis, but nothing new was uncovered. The patient was then returned here for restudy. On his third admission a thorough investigation was again undertaken, and this time it was learned from the patient that he was taking an expectorant, prescribed by a medical consultant for his asthma during his second admission. Elimination of this medicine was followed by a gradual complete clearing of his dermatitis. The original diagnosis in this case was undoubtedly correct, but when the patient was finally removed from contact with the initial irritant his skin eruption was perpetuated by a medicine which he ordinarily would probably have tolerated with impunity. This may be regarded as an example of synergy, but it demonstrates the value of a case review. Often, however, in spite of much study no new elements are found, and if malingering is excluded it must be assumed that the initial sensitization is still responsible for the prolonged eruption.

The physician is frequently called upon to give an opinion regarding the advisability of returning a worker to the same job at which he originally suffered a dermatitis. The physician's attitude in such cases is this: All persons who have had a severe occupational dermatitis and who could not get well while at work should never again return to that work. Experience has taught that such a worker has a good chance of recurrence, and the second attack may be more severe and of longer duration than the first. The problem is often a difficult one to decide, especially in the case of skilled workers who will suffer financially in seeking new employment. As a rule, the worker is advised not to return to his old job. However, there are always those that do, suffer no recurrence, and then return to chide the doctor on his apparently erroneous diagnosis. But on the other hand, many who return to work against advice experience severe flare-ups with subsequent long periods of disability. Statistics on this phase of the subject show that the chances for and against recurrence in such situations are about equal with recurrence being favored. The length of exposure before the onset of sensitization is important. Those with a comparatively short exposure are less liable to experience a recurrence than those whose dermatitis first appeared only after a long exposure. The physician's admonition against return to work serves the best interests of all concerned. The worker, his employer, and the insurance carrier must weigh the chances and assume the risk if the patient returns to his former job.

If by having a dermatitis a worker has gained a better understanding of the hazards involved, it may be possible for him to resume his work without further difficulty. This is especially so if it has been demonstrated to him that a definite substance was responsible for his dermatitis. A stitcher in a shoe factory here developed a dermatitis of the forearms. The history disclosed that a liquid wax, thrown from the fast moving thread, was continually splattered on his forearms as he sat at his machine. A patch test with this wax was definitely positive. The patient was discouraged from continuing with such work; but being unable to find a job which paid an equal wage, he decided to return to his former employment. However, forewarned is forearmed, and this time he avoided contact with the wax as much as possible. He kept his sleeves rolled down, changed his shirt every day, and washed his hands frequently. By these simple precautions he has been able to carry on for the past several months without any signs of recurrence.

The prevention of industrial dermatitis requires concerted effort by all industries and is the only solution of this costly problem. Various industries have undertaken such programs with outstanding success. It remains now for others to copy them, and in so doing the following suggestions might be considered. An industrial nurse should be engaged by all large industrial plants. By being present on the spot she gradually develops experience of inestimable value in the recognition of early cases. Such a service alone more than justifies her presence, but she also serves in many other ways. Periodic instruction of the workers in the hazards of their industry by lectures and demonstrations is important. Posters and constant supervision by foremen are also necessary reminders. Washing and bathing facilities must be available, and ample opportunity should be provided for the worker to clean himself, preferably on company time. Cleanliness in the working environment is no less important than personal cleanliness. Special efforts should be directed toward keeping the work rooms and machinery as free from grime and dust as possible. All unnecessary hazards must be detected and eliminated. Gloves or protective creams should be used wherever

it is impracticable for mechanical devices to replace manual contact. Work which requires continual wetting of the hands should be interrupted during the day by intervals at dry jobs. Exhaust hoods should cover all processes emitting dangerous fumes, or better yet, these processes should be totally enclosed. Safety rules must be enforced and violations not allowed to pass unnoticed. Consideration of the possible deleterious effects on the workers should precede the introduction of new substances into industry. Dangerous chemicals such as benzene should not be preferred because of their low cost. Less dangerous substances such as naphtha and alcohol serve equally as well. Where necessary, protective clothing should be furnished and kept clean by the company. The rotation of workers at different jobs on a weekly or monthly basis is not considered advisable since thereby only a greater number of workers are subjected to the chance of sensitization. And finally, large industrial plants should maintain active rehabilitation programs to train the sensitized worker in a new job which approaches his former wage level.

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Streptomycin Controls Abandoned

The last remaining wartime controls over streptomycin were rescinded by the Office of Materials Distribution, Commerce Department, effective July 6th. Only export controls remain under war control order M-393. Production of streptomycin increased from approximately 3,000 grams in September 1945 to more than 550,000 grams in May 1947. In March 1946, approximately 27,000 grams were produced and allocated by CPA to the Army, Navy, Veterans Administration and the U. S. Public Health Service, and for research purposes. Small amounts of the drug, taken from the research allocation, were granted on appeal for treatment of civilians. Limited commercial distribution of streptomycin for civilian use was first authorized in September 1946. Some 1,600 general hospitals throughout the country were selected as depots to receive the drug and to supply other hospitals in their areas. By that time, monthly production was about 150,000 grams. As production was stepped up, increasingly larger amounts of streptomycin were made available for civilian use.

——From *American Druggist,* August 1947.

After indicating the high mortality rates to be expected in bulbar and bulbospinal cases of poliomyelitis, the author outlines the therapeutic management of these patients in an effort to reduce the death rate.

Treatment of Bulbar Poliomyelitis*

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The United States during the past four years has experienced its worst four years of infantile paralysis. If any reduction in the mortality due to infantile paralysis can be expected it must be accomplished by a reduction in the mortality of the bulbar and bulbar-spinal cases of poliomyelitis.

Most physicians will agree with me that a large proportion of cases of the mild spinal type of poliomyelitis will make relatively good response to any therapy, be it hot packs, splints, muscle therapy or a combination of methods. However, there is no such wide choice with reasonable chance of favorable outcome in the handling of bulbar and bulbar-spinal cases. These individuals must be handled as "true medical emergencies" and all of these cases require special consideration in the procedures enumerated below.

TABLE 1

*Summary of Cases by Type, Deaths and Fatality Rates**

	1943	1944	1945	1946	TOTAL
Total Cases	264	367	413	256	1300
Deaths	21	12	39	16	88
Fatality Rate	8%	3.3%	9.4%	6.2%	6.8%
Bulbar (16%)					
Cases	60	34	83	30	207
Deaths	14	7	21	6	48
Fatality Rate	22.3%	20.6%	25.3%	20.0%	23.2%
Bulbar-Spinal (4.8%)					
Cases	16	10	22	15	63
Deaths	6	3	11	9	29
Fatality Rate	37.5%	30.0%	50.0%	60.0%	46.0%
Spinal (79.2%)					
Cases	188	323	308	211	1030
Deaths	1	2	7	1	11
Fatality Rate	.53%	.62%	2.3%	.47%	1.1%

* 1943 and 1946 cases occurred in Cook County.
1944 cases occurred in Hickory, North Carolina.
1945 cases were from the Rockford, Ill., area.

* From the Cook County Department of Public Health, Chicago, Ill.

Presented at the Annual Session of the American College of Physicians, May 2, 1947.

Since the high mortality of infantile paralysis cases seems to fall in the bulbar and bulbar-spinal type of cases, the care which must be given these cases must begin immediately upon diagnosis of the disease and be continued without interruption until the life of the victim has been saved. The following routine of treatment set up in these epidemics for the care of bulbar and bulbar-spinal cases of poliomyelitis is based upon the most recent knowledge of the behavior of this disease.

Transportation. When a case of bulbar poliomyelitis is diagnosed by a physician that patient should be placed in a position where the head is lower than the rest of the body thus allowing for postural drainage of the saliva from the mouth. It must be realized that the patients with bulbar poliomyelitis cannot swallow, cannot expectorate, cannot cough, and if they are placed in a semi-sitting position and transported in this manner they may aspirate saliva, which at times may cause death. I have seen this unfortunate situation occur on several occasions. These patients should be placed in an ambulance with the head lower than the rest of the body and a suction apparatus or rubber suction syringe should be available to aspirate the mucus out of the mouth if necessary. Transportation of patients with bulbar poliomyelitis over a long distance is not recommended. Excessive speed and the use of the siren which may excite the patient is also not recommended. The smoothest, slowest, road to the hospital should be used. The patient should not be subjected to any strain or agitation and the patient's morale should be maintained at all times.

Spinal Puncture. During the polio season and especially in areas where there is an epidemic any procedure which would excite and aggravate the condition of a patient with bulbar poliomyelitis should be avoided. Spinal puncture is not recommended during the early stage of the disease. At a later time when the patient seems out of danger, if a spinal puncture is desired, it can then be done without harm to the patient.

Examination of Patient. In the bulbar cases of poliomyelitis the primary interest is to save the life of the patient. Only sufficient examination should be made to make a satisfactory diagnosis and that should be completed in as short a time as possible. Most of the time this diagnosis can be made by the presence of a fever and rapid pulse rate, signs of meningeal irritation, nasal voice, inability to swallow, inability to cough or expectorate, co-existing facial paralysis or other cerebral motor palsy, and by marked excitability or prostration.

Position of Bed. Patients suffering with bulbar or bulbar-spinal polio should lie on a specially prepared bed where a solid board plus the presence of a hard mattress will give the patient firm support. The foot of the bed should be elevated 15° to 20°. This elevation will permit easy aspiration of the mucus with a catheter and suction.

Tracheotomy. The decision whether or not a patient can be benefited by a tracheotomy is a very serious matter. A tracheotomy may be of great value when the patient has a continuous problem with his salivary and bronchial secretions. In a recent epidemic, the combination of tracheotomy, respirator, helium and oxygen were used to good advantage in the saving of human life. I have observed several almost miraculous recoveries following tracheotomy, while on the other hand I have seen a few fatalities immediately after surgery. I feel, however, that if there is a consistent "drainage" problem of the salivary and bronchial secretions a tracheotomy should be done.

Nursing Care. Every patient who has any degree of swallowing difficulty must be attended at all times by a nurse especially trained in the care of bulbar poliomyelitis. Proper aspiration of mucus by the nurse is essential at all times. The quieting influence of a nurse on the extremely ill and apprehensive patient is essential.

Serum and Parenteral Fluids. Although the specific value of convalescent serum in bulbar poliomyelitis is debatable there appears little doubt that this agent used in large amounts early in the course of the disease is of value in maintaining the patient's normal physiologic state. There is increasing evidence that virus diseases may be treated with specific sera.[1] In my experience, I have observed favorable clinical response when large amounts of convalescent serum are given early! At least 300 to 600 cc. of serum or plasma should be used as early as possible, preferably within the first 48 hours of disease, the dose being dependent upon the age and weight of the child. It is preferable that the patient should be kept at all times on the slightly dehydrated side rather than that he be given an over-abundance of fluids. In some cases concentrated plasma or serum albumin diluted to one half or one third of normal dilution has been found to be of great value. If there is difficulty in swallowing oral administration of fluids should not be attempted in the acute stage. If there is a great deal of cerebral edema, excessive amounts of saline solution should not be used and 10 per cent glucose should be used alone. If there is no evidence of cerebral edema, 5 per cent glucose and saline may be given to maintain fluid balance. Subcutaneous or intramuscular fluids are contraindicated.

Supportive Therapy. Protein hydrolysate with dextrose 5 per cent has been found very useful in chronic bulbar cases where a patient is not able to maintain his own weight. This medication can be given in large amounts if it is given slowly. In prolonged treatment of poliomyelitis, especially where heat may be used during the course of therapy, administration of the four critical water-soluble vitamins is indicated. Thiamine hydrochloride, riboflavin, niacinamide and ascorbic acid, constituting the basic formula of vitamins first described simultaneously by Spies [2] and Jolliffe and Smith [3] in March 1943, should be supplied to the patient early either intravenously, intramuscularly, or by mouth if possible.

Suction. Suction apparatus such as used in tonsillar operative procedures or continuous nasal suction with a permanently placed catheter should be made available. In the author's experience intermittent suction is preferred if the nurse is properly qualified in its use. The patient should lie on his side, so that the mucus may accumulate in the patient's cheek. The intermittent suction applicator can in this position aspirate the mucus very easily without irritating the back of the throat and without producing gagging. The nurse should be trained for all emergencies regarding proper removal of saliva and mucus from the mouth and throat.

Oxygen should be supplied as promptly as indications, such as cyanosis or rapid respiratory rate, develop. Oxygen tents in my experience have proved much more preferable than nasal oxygen. If nasal oxygen is administered over a long period of time the catheter may produce nasal irritation, congestion and discomfort.

Sedatives. No narcotics should be used in the treatment of bulbar poliomyelitis at any time. If sedatives are necessary small doses of one of the phenobarbital group are preferable. Every effort should be made by the nurse and the hospital personnel to reduce excitement, excessive noise and any unnecessary

disturbance. The nurse must reassure and quiet the patient by expert handling.

Position of Rest. Patients with bulbar poliomyelitis usually prefer to lie on their back. Over a prolonged period of time this position is rather tiring and the patient should be turned on his side by the nurse and properly supported by pillows. Patients may actually prefer this position. If there is any associated difficulty in breathing or loss of power in the intercostal or diaphragm muscles, the patient should not be allowed to lie on his abdomen.

Hot Packs and General Care. No added treatment should be started on any patient with bulbar poliomyelitis until the acute stage is over. Hot packs, physiotherapy exercises, the giving of fluids by mouth, etc., should be delayed until the temperature is normal for at least 24 to 48 hours. Enemas should be used early depending upon the condition of the patient and the presence of intestinal discomfort. The patient's pulse and temperature should be noted frequently and the patient should be covered and kept warm at all times. No attempt should be made at any time to give carbonated beverages, grapefruit, orange, tomato, or other juices during the acute febrile stage. Water is preferable until satisfactory adjustment can be made to swallowing.

CONCLUSIONS

1. Some 1,300 cases of acute anterior poliomyelitis occurring in four consecutive years in epidemic areas have been classified by area. Of this total 207 were of the bulbar type, 48 of which proved fatal for a fatality rate of 23.2 per cent. Another 63 were of the bulbar-spinal type, 29 of which proved fatal for a fatality rate of 46.0 per cent. The other 1,030 cases were of the spinal type, 11 proving fatal for a fatality rate of 1.1 per cent.

2. This study reveals that the fatality rate of any epidemic is directly proportional to the percentage of bulbar and bulbar-spinal cases.

3. In the epidemics where the incidence of bulbar and bulbar-spinal cases was low, the disease seemed to be milder and the fatality rate lower. Where the incidence was high, the bulbar and bulbar-spinal cases were more severe and the fatality rate higher.

4. Because of the high fatality in bulbar and bulbar-spinal cases this group requires expert, early, and unremitting medical and nursing care.

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Training in Tuberculosis

Veterans Administration will offer physicians residency type training in tuberculosis for the first time in its history, Dr. Paul R. Hawley, VA's chief medical director, announced.

The training program was approved by the American Medical Association.

Five VA hospitals where training will be available are in Brecksville, O., Alexandria, La., Excelsior Springs, Mo., Oteen, N. C., and McKinney, Texas.

Although the hospitals at Alexandria and Oteen are not now associated with medical schools under the VA Deans' Committee plan, physicians serving there may earn credit toward the examinations of the American Specialty Board for Internal Medicine and its sub-specialty board for tuberculosis.

The other three VA hospitals are affiliated with medical schools under the Deans' Committee program.

Following the experimental work on renal ischemia as a cause of hypertension and with the advent of sympathectomy in management, there has been renewed interest in this most common disease. In this paper consideration is given to the role of the psyche in hypertension, a factor that every experienced clinician has seen at work in many of his hypertensive patients.

Psychosomatic Aspects of Arterial Hypertension*

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High blood pressure and arteriosclerosis are the greatest cause for serious disability and death in our modern civilization. It has been reliably estimated that one half of all people over the age of 45 will die of one of the cardiovascular-renal diseases. Essential hypertension makes the greatest contribution to this group of disorders.

Our knowledge of the circulatory disorders has progressed in hundred-year cycles. It was about 1633 that William Harvey reported on the nature of the circulation and about 1733 that Stephen Hales, an English pastor, demonstrated the phenomenon of blood pressure in the horse. In 1833 Richard Bright correctly concluded that an increase in the peripheral resistance caused enlargement of the heart in patients with "chronic granulation of the kidneys," and about 1933 Goldblatt, by his brilliant researches, produced for the first time in the experimental animal a form of hypertension which corresponds closely to essential hypertension in man.

What have these remarkable observations contributed to the practical management of the individual who has high blood pressure? Not a great deal, I fear, because we are still ignorant as to the cause of hypertension and there is little we can do to eradicate it. In a sense, all that has happened is that the old argument over whether hypertension or systemic arteriosclerosis came first has been narrowed down to the kidney—which comes first, hypertension or arteriosclerosis of the renal vessels? More and more evidence is accumulating to suggest that hypertension precedes arteriosclerosis, but that still leaves us very much in the dark as to what initiates the hypertension.

What is the relation of psychosomatic medicine to this subject. While psychosomatic is a new term, it describes an approach to medicine as old as the art of healing itself. It is not a new specialty but rather a point of view which applies to all aspects of medicine and surgery.[1] It connotes the simultaneous application of physiologic and psychologic technics in the study of illness. It does not mean to study the soma less; it only means to study the psyche more. Its subject matter is founded on the important advances in physical medicine as well as on the biologically oriented psychology of Freud. It is not a new discovery, but rather a reaffirmation of the ancient principle that the mind and the body are interactive and interdependent, a principle that has always guided the intelligent general practitioner. Indeed the traditional old family doctor very often was an excellent psychosomatic physician, although he never thought of himself as such. His patients usually were intimate friends, and he was familiar with their social situation, as well as with their psychologic and physical peculiarities. He was well aware that these factors were related to illness. As a science, psychosomatic medicine aims at discovering the precise nature of the relationship between the emotions and bodily disturbances. Psychiatry was established on a firm scientific basis in World War I, and World War II has seen its more complete integration into general medicine. When that integration is complete there will be little need for the term psychosomatic; good medicine will be psychosomatic medicine.

How can we relate psychosomatic medicine to hypertension? It is generally admitted that psychic factors play some part in essential hypertension. Thus, it is always emphasized that we must allow for the emotional element in individual blood pressure readings. It is also well known that rest and reassurance play a large part in the medical management of hypertensive patients, both in relief of symptoms and in reduction of the blood pressure level. The early symptoms of hypertension are often exactly those of a psychoneurosis. Emotional stress at times seems to precede the onset of hypertension, and anxiety bears a close relationship to the aggravation of existing symptoms in hypertension. Personality study often

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reveals a deep-seated conflict which stands in close relationship to this anxiety.

PSYCHOSOMATIC ASPECTS OF ETIOLOGY AND PATHOGENESIS

Two psychic tendencies seem to stand in close relationship to hypertension, anxiety and rage. Essential hypertension is one of the commonest disorders of civilized life and anxiety states are certainly no less common. Therefore, simply from the standpoint of their frequency, it is not surprising that the two are often present in the same individual. But the question which interests us is this, Is there a more specific relationship between the two?

It has long been known that anger is an emotion connected with high blood pressure. How often people remark to a person who is angry, "Now watch your blood pressure." However, psychoanalytic studies suggest that hostile impulses of which neither the individual nor the casual observer is aware may also have an important influence on the blood pressure. In other words, long-continued, repressed rage may manifest itself through the circulatory system by elevating the blood pressure. Alexander,[2] Saul,[3] and Dunbar[4] all call attention to the unresolved psychologic conflicts which give rise to chronic emotional tensions, and these, they feel, are specifically related to the hypertension. The psychic factor thus becomes one of the multiple factors that enter into the pathogenesis of hypertension. An anology might be drawn to the role of the kidney or the endocrine glands, either of which, in rare instances, may be chiefly responsible for the presence of hypertension but in most instances seems to play a secondary role, depending on a constitutional or inherent tendency. The psychologic factor is only one phase, although an important phase, "in the composite of the degree and kind of renal, endocrine, and nervous participation."[5]

PSYCHOSOMATIC ASPECTS OF THE CLINICAL PICTURE OF HYPERTENSION

Ayman and Pratt[6] showed that many of the symptoms of patients with essential hypertension closely resemble those seen in patients with psychoneurosis without hypertension. Closer study of their patients revealed that they really were suffering from psychoneurosis as well as hypertension. In a more recent paper Ayman[7] divided the symptoms of essential hypertension into three groups:

1. Psychoneurotic symptoms
2. Vasospastic symptoms
3. Organic symptoms

Headache and various forms of head discomforts, dizziness and constipation, as well as precordial pain, breathlessness of the sighing respiration variety, and fatigue often cannot be explained directly on the basis of the hypertension. They are out of proportion to the disease. When such patients are studied from a psychosomatic point of view it is often found that there is a great deal of conflict in their makeup and an inability to express their aggression directly, and thus it would seem that tensions which cannot be adequately expressed in words or action seek their way out in the circulatory system by means of body language. We must repeat that psychologic factors are not the only ones of importance in the clinical picture of hypertension, but they are important because their modification often results in benefit to the patient, regardless of whether the blood pressure figures are lowered or not.

Ayman suggests that generalized arterial constriction may be responsible for symptoms. It would seem to be largely a question of the intensity of the process and the rapidity with which it appears. Ayman points out, and we have frequently seen, patients with very high blood pressure, 250–300 mm. systolic, which may exist for years without symptoms. Yet in other individuals with lower pressures of more sudden onset severe headaches, dizziness, spells of blushing and pallor, temporary pareses and even convulsions seem to appear on the basis of vascular spasm.

When the hypertensive vascular disease advances and vital organs are affected, it is of course true that many symptoms are caused by failure of these organs. Even here, however, it is important that we evaluate the part played by emotional as well as physical factors.

Headache. Janeway[8] observed that headache was the most frequent symptom of which his hypertensive patients complained. He described the typical hypertensive headache which appears on awakening as consisting of sensations ranging from a dull ache to severe pounding distress and as usually being located in the cervico-occipital region. But in addition, he noted that a surprisingly large number of patients had been subject to migraine throughout life. Gardner, Mountain, and Hines[9] found migraine five times as frequently in hypertensive patients as in a control group. Then there are a great variety of head pains, discomforts, and peculiar sensations, such as dullness and fullness with or without vertigo, which occur in hypersive subjects and are often referred to as headaches. The tendency is to attribute all these "headaches" to the hypertension. Certainly elevation of the blood pressure seems responsible for the so-called typical

hypertensive headache. (Even here, however, the anxiety factor enters insofar as it is related to exacerbations of blood pressure.) However, the vast majority of peculiar head sensations and discomforts often designated as headache cannot be correlated with the blood pressure level itself. Here the emotional factor is directly related to the peculiar head sensations.

Recently I studied a patient with severe hypertension and constant headache. She had had a complete physical study. The blood pressure averaged 200/120. The heart seemed within normal limits as to size, as determined by the orthodiogram, and the electrocardiogram indicated only left-axis deviation, other features being within the limits of normal. There was no evidence of impairment of cardiac function. The eye-grounds showed arteriosclerosis of the hypertensive type, grade 1, but no evidence of retinitis. Urinalysis was negative and renal function, as measured by the urea clearance test, was within normal limits. An intravenous urogram was normal. The conclusion was essential hypertension with symptoms out of proportion to disease.

After reviewing the studies, I said to her, "Sometimes tension is related to hypertension." She thought that over for a moment and said, "Well, I can improve on that formula. In my house, it is 'contention-tension-hypertension.'" Then she went on to tell of the role she played as a "buffer" between an irate husband and a lazy son who was in business with his father and of the constant quarrelling between them. The greater part of her sympathy was with the son. She always was trying to shield him. She was a martyr-like person and that kind always pays a penalty, absorbing punches which produce symptoms. This woman's headache was the "body language" means of representing her difficult life situation. It was just as if she would say, "My husband is a headache to me." Indeed he was. He was having an extramarital affair and boasted of it openly. He felt that it was indecent to smoke or drink, but the sexual appetites were normal and were to be indulged and no secret was to be made of the fact. By thus humiliating her in the presence of her friends he added to her problem. Perhaps as a result of the uncritical way this information was received she gained enough confidence to present her husband with an ultimatum and, contrary to her worst expectations, he agreed to end the extramarital affair. It made a great difference in her life. Thereafter, she was well as far as headache was concerned. It is true that this patient still has her hypertension. But the disappearance of the headache was an indication that the symptom was out of proportion to the disease and was related to the anxiety. The anxiety in turn was related to emotional conflict and the conflict could be understood by getting to know the patient as a human being and not just as a medical case.

Migraine presents a more complicated mechanism. It can hardly be assumed, as in the case of anxiety and hypertension, that migraine is so frequent in hypertension because the two are common disorders and therefore must frequently meet. Instead, there seems to be a common denominator, and psychologic study gives a clue. Apparently there is an intimate relationship between the personality structure of the two disorders. Both present evidence of chronically repressed rage. Attacks of migraine occur when situations are met which intensify the rage without providing opportunity for adequate expression.

Constipation. Most patients with hypertension see a connection between headache and bowel function. When they suffer from constipation they are ill, and when the bowel moves freely they are speedily relieved of symptoms. This, of course, is true for many patients who do not have hypertension, but in hypertensive individuals the relationship is especially obvious. Moreover, it is a relationship which is easily exploited and in which the physician becomes a pathogenic agent when he focuses attention on the bowel, as in the days, fortunately not now so common, when colonic irrigations were frequently prescribed for "autointoxication." It is very difficult to overcome a patient's prejudices—and even those of the medical profession—in this regard. But it does seem to be largely a psychologic association, because relief comes too quickly after a bowel movement to be ascribed to physical causes, and, in addition, deeper psychologic study often shows the relationship between ideas of obstruction "poisoning," and pain in the head.

Vertigo. Patients frequently refer to the symptom of vertigo, which occurs in a great many instances with the head discomforts just described, as dizziness and giddiness. Differentiating syncope, which does not imply a disturbance of equilibrium, and true Ménière's syndrome, one often finds that the symptom of vertigo bears a definite relation to an anxiety state. Frequently in association with ringing in the ears and sometimes with numbness and tingling of the extremities, it is the result of psychic stress.

The early symptoms of anxiety are usually expressed through the cardiovascular, respiratory, gastrointestinal, and genito-urinary systems. It is after the anxiety state has persisted for some time that the symptom of vertigo makes its appearance. When it occurs in association with hypertension the vascular disease often is held to be responsible. However, it

is well to bear in mind that, like organ language elsewhere, vertigo (unsteadiness) frequently is the symbolic representation of insecurity, and this is just as true when it occurs in association with hypertension.

Cardiac Neurosis. Pain in the precordium, palpitation, dyspnea and fatigue are a group of symptoms frequently associated with cardiac neurosis. Fatigue may be a prominent part of the clinical picture, in fact, the most prominent symptom, although again and again the patient speaks of pain in the heart region and only after considerable discussion is it brought out that really the most important symptom is fatigue, that it occurred first, and that only later was the pain added. One of the commonest causes of fatigue is emotional conflict, which steals energy which then is not available for useful purposes.

When these symptoms are present with a normal cardiovascular system and the general medical examination otherwise is negative, it is not as a rule difficult to assign them to their proper sphere—the emotions. When hypertension is present, however, it is almost invariably held to be the responsible factor. It is under such circumstances that psychosomatic study will frequently reveal that symptoms are out of proportion to disease, that there is much conflict in the personality makeup, and that it depends on repressed hostility. Moreover, a specific as well as a temporal relationship will be found between the onset of the symptoms and a psychic event.

Thus in regard to symptoms in association with hypertension one must always question their relation to the high blood pressure itself and make an effort to understand them from the viewpoint of behavior.

PSYCHOSOMATIC ASPECTS OF TREATMENT

The knowledge that "every psychic tendency seeks adequate bodily expression" gives a practical hint in dealing with hypertensive patients. An explanation to the effect that inner tension which cannot be released through ordinary channels (action or words) may manifest itself in the circulatory system by adding to the problem of hypertension represents a rational approach insofar as the patient is concerned. This often leads to a discussion of problems which are of considerable interest and importance from the standpoint of illness.

A recent case, reported in detail elsewhere,[10] is interesting from this standpoint. The patient, a young man working for a trucking company in Philadelphia, had rather severe hypertension. His father had worked for the same organization, was killed in an accident, and the family denied compensation. Our patient was "burned up" about it. He wanted to get into union activities where he would have an opportunity to avenge his father. He had been denied this opportunity because it meant "too much work and excitement." We gave him permission. In addition to working eight hours on the job, he had to work six hours for the union. He was an organizer and worked hard, yet he actually improved during the two years he was engaged in union activities. He improved as far as symptoms were concerned and even his blood pressure was lower. Then the union broke up and again he was "burned up." He was "choked with rage," and his blood pressure went up again. As soon as he was denied an outlet for aggression along the lines of avenging his father, up went his blood pressure and symptoms returned. So I think there is something in the personality of a hypertensive patient that suggests a relationship between hostile impulses that cannot find an outlet and elevation of blood pressure. It is not the whole answer—not by any means. I do not maintain that it is the basic cause of hypertension. A patient can be "burned up" all his life and unless he has a predisposition to hypertension, he probably will not get it. Given the predisposition and an aggressive personality with no outlets for aggression, then in all probability, hypertension will develop.

The psychosomatic concept of pathogenesis and the clinical picture must impress us with the necessity for the total evaluation of the patient with hypertension. This requires more than lip service to the concept of the organism as a whole. It represents a combined physical and psychologic study. Because incapacity often is out of proportion to the disease it will be found important in a great many patients to re-educate them along the lines of "carrying on" rather than to urge rest and more rest. Menninger[11] advances this idea on the basis that self-directed aggression may be turned outward by the authority of the physician and that extroversion of the aggression, if not too strenuous, may be of advantage to the patient.

In a great many patients with hypertension, instead of cautioning rest and more rest, we must free them from the phobia of their high blood pressure and allow them to express their aggression along more nearly normal channels.

There is no objection to the effort to lower blood pressure as long as this does not constitute the sole approach to the problem of high blood pressure. This applies to the most recent method of dealing with hypertension by surgical means. In some patients sympathectomy will produce a prolonged drop of the blood pressure. One may say to patients who have hypertension and anxiety (due to the meeting of in-

ner conflicts and external pressures) that our objective in their management is to "take off some of the load." If we can do this by helping them to achieve some insight into their emotional problems, with consequent lowering of tension, well and good; if we can do it by environmental manipulation, fine; but if we have to resort in addition to drug therapy (thiocyanate) or to surgery (sympathectomy) by all means let us use a combination of efforts to help our patients with hypertension. While I believe that essential hypertension cannot be eradicated by any psychotherapeutic process, no matter how intensive or prolonged, I also feel that almost every patient with essential hypertension can be benefited by psychotherapy.

Binger and his associates [12] in recent studies have the following to say: "The problem is that of treating a severe character neurosis in which anxiety, depression, and suppressed aggression are the cardinal psychopathological features. The method of choice will vary from cheerful neglect to deep psychological exploration. The latter . . . is a matter for the expert. What is to be hoped from it we cannot say. There is as yet no evidence that psychoanalysis or any other psychotherapeutic procedure can reverse the physiological process or change the destiny of this disease—be it benign or malignant. The problem is an open one. It needs further investigation. The ground has now been cleared for such an undertaking."

Another aspect of the problem is referred to by Page and Corcoran [13] who call attention to some of the well known facts regarding the superficial aspects of the relation of the emotions to hypertension and then state: "Such observations, however thoroughly documented, merely establish mental disturbance as coordinate cause; they do not suggest that it can be a primary cause of the whole disease. To establish it as a primary cause, it must be shown (1) that hypertension can arise *de novo* as a sequence of a characteristic mental pattern or (2) that the disease as act and potentiality can be abolished by appropriate psychotherapy."

Although the psychosomatic approach does not offer a complete solution of the hypertensive problem and does not even apply to all patients, it is a practical method of dealing with a set of important factors that may be modified, whereas the constitution of the individual cannot be touched. It is an approach heretofore not sufficiently practiced. We are too much concerned with physical measurements in hypertension—the blood pressure figures, the size of the heart, the electrocardiogram, the amount of retinal sclerosis, the percentage of renal function, the urographic study, the renal blood flow, all of which are essential in the study of the hypertensive person but give incomplete information from the standpoint of the total evaluation of the patient. They should represent the beginning and not the end of the study. We have been too little concerned with emotional life, which may hold the key to the satisfactory management of the hypertensive patient.

SUMMARY AND CONCLUSIONS

The organic tradition in medicine has been responsible for a narrow view of the etiology and treatment of essential hypertension. The psychosomatic approach does not neglect the physical problems involved but includes a consideration of the role of the emotions. It does not mean to study the soma less; it only means to study the psyche more. It emphasizes the multiple factors in etiology and pathogenesis and attempts to evaluate the resulting composite clinical picture. Such studies indicate that emotional factors apparently are intimately related to the development of hypertension in some patients, to the production of symptoms in many others, and enter into the question of treatment in nearly all patients with essential hypertension.

A common problem seems to be the presence of emotional tension due to chronic repressed hostility. This inhibited aggression (chronic rage) seems to bear a definite relationship to hypertension and if it can be relieved by means of psychotherapy anxiety is diminished and blood pressure is often lowered. Even if the blood pressure is unaffected, the treatment often benefits the patient by making him a healthier and more effective personality. Our objectives in treatment should be readjusted. We must not limit our efforts to "bringing the blood pressure down." There is no reason why we cannot combine physical (medical and surgical) methods with psychotherapy but we must go beyond the physical aspects of hypertension to the personality of the hypertensive individual in order to be successful in the management of such patients.

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BOOK REVIEWS

PENICILLIN THERAPY: Including Streptomycin, Tyrothricin and Other Antibiotic Therapy. By John A. Kolmer, M.D. Second Edition. 339 pages. New York, Appleton-Century, 1947. $6.00.

In the preface the author points out that this volume has been written for the practitioner of medicine and therefore much of technical nature relating to the production of the antibiotics has not been included. Nevertheless he has included those technical details having to do with assay of antibiotic levels in body fluids since this is necessary for clinical laboratory technicians and to the physician following the progress of a case under treatment.

The first chapters are devoted to a brief description of chemotherapeutic agents of biologic origin, their mode of action, the background of and the history of penicillin. Methods for detection and assaying penicillin by both the Oxford cup, the serial dilution and Fleming slide cell are described in detail. These are helpful for the clinical pathologist or clinician doing his own bacteriologic work. The chemical and physical properties of penicillin are considered and the partition forms of F, G, X and K. The production of penicillinase by bacteria is touched upon, of importance in mixed infections where such substance may inhibit full penicillin effect.

Several chapters follow covering selective activity of penicillin for various infectious agents, natural resistance of certain strains of susceptible organisms, acquired resistance of bacteria to penicillin as well as the mechanism of the effect of penicillin upon bacteria and other living causes of disease. The penicillin unit level in the serum after the various routes of administration, intravenous, intramuscular, oral, etc. is set forth. The author also discusses its diffusion from the blood into other body fluids, into exudates, as well as the excretion and fate of penicillin. The effect of prolonging absorption (by beeswax and oil) and its excretion is considered. The untoward effects of penicillin upon the patient, both local and general are described.

Coming to the clinical application of penicillin Kolmer indicates the need for bacteriologic examinations if possible to evalue its expected effect. He considers indications, contraindications and describes the modes and routes of administration.

Separate chapters deal with the use of penicillin in the septicemias and subacute bacterial endocarditis; its use in the several forms of coccal meningitis, brain abscess and wounds to the brain are covered. The chapters on the use of penicillin in diseases of the eye, ear, nose, and throat differentiate those diseases usually responding to penicillin from those which do not and indicate why the latter do not respond. The efficacy of penicillin in the coccal pneumonias and in the prevention of and treatment of empyemas when established, and the variability in causing improvement in chronic bronchial diseases and lung abscess is the subject matter of a separate chapter.

The author gives much prominence to the penicillin therapy of gonococcal infection because so much information has been accumulated on the subject. The method of treatment, criteria of cure, the masking or suppression of syphilis, and the handling of complications of gonorrhea are presented adequately. In the chapter on the use of penicillin in syphilis, Kolmer abstracts the literature on the subject quite completely as of the date of the writing of the manuscript. *Penicillin treatment of skin diseases* is presented very briefly.

Under the surgical diseases are covered such subjects as the prophylaxis of infection and local disinfection in wounds, accidental or operative, by the

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The general practitioner can readily attest to the anxiety of the parents in cases of epiphora of the newborn. This brief note clearly sets forth the problem.

Practical Notes on Epiphora in the Newborn

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Although the condition of epiphora in the newborn is not exceedingly common, it is seen with sufficient regularity in the office of the ophthalmologist to warrant a short review of its characteristics and treatment. Very seldom is the oculist the first to be consulted. Almost all of the cases are first seen and treated by the obstetrician, pediatrician or general practitioner who has been concerned with the birth of the child and its postnatal care. The cases seen in the office of the eye physician adhere closely to a definite pattern, the major point of similarity among them being prior and totally ineffective treatment of the eye by antiseptic drops or ointments. The condition is not serious but occurring, as it does, so shortly after birth is likely to cause anxiety and concern to the parents. Properly treated it responds very quickly and such response is of great satisfaction to the parents and the physician.

Despite the fact that the condition is present at birth, the epiphora may be masked for the first several days by redness of the eyes caused by use of silver nitrate drops at the time of birth or local trauma to the eye incident to birth itself. When, after several days, the eyes should have returned to normal appearance, it will be noted that there is a clear discharge from the eye accompanied by crusting of the palpebral margins without involvement of the conjunctiva. It is most often unilateral. Complications such as chronic conjunctivitis, ulceration of the cornea or nonulcerative keratitis seem to be extremely rare.

The treatment of epiphora of the newborn depends on an understanding of the embryology of the lacrimal drainage apparatus. The lacrimal sac and nasolacrimal duct develop from a buried cord of ectodermal tissue which is later canalized and lined with epithelium. This cord is found in the fetus to lie between the maxillary and lateral nasal processes. Prior to birth, as a result of canalization of this cord, the lacrimal sac may be filled with epithelial debris. It is this debris which causes the obstruction and which is the chief factor in epiphora in the newborn. A more serious type depends upon the presence of an anatomic barrier at the base of the sac in the form of a thin membrane. This requires a somewhat different therapeutic approach which will be described later. Cases of congenital absence of the lacrimal sac and other anomalies are too rare for consideration in this brief report.

When these patients are finally seen by the ophthalmologist they almost without fail give a history of having been treated by the local instillation into the conjunctival sac of ophthalmic ointments, such as yellow oxide of mercury or sulfathiazole. When one considers the real cause as outlined above, it can be seen that such therapy will accomplish nothing but the waste of time. The proper treatment is very simple and is outlined as follows:

1. Manual milking of the sac by the thumb is the method of choice. This is done by pressing the thumb over the area of the lacrimal sac and milking toward the eye. This procedure should be repeated three times a day by the mother and results in the expression of the epithelial debris from the lacrimal sac.

2. Penicillin eye ointment should be applied locally to the affected eye for the purpose of combating the low-grade blepharitis and as a general prophylactic.

The result of this form of therapy is exceedingly gratifying and is often noted after only 24 hours. Occasionally one will see, as a complication, a dacryocystitis, but this is not common.

The few cases which do not respond to this treatment can be considered to be suffering from a type of anatomic barrier and are managed in the following manner. Under light ether anesthesia, a Bowman lacrimal probe, size No. 6–No. 8, is passed through the upper punctum into the lacrimal sac. Prior to this, the canaliculus will have to be slit by the appropriate instrument. The probe is passed into the lacrimal sac, through the occluding membrane and into the nasolacrimal duct. This is followed for several

days by milking of the sac and by the use of a suitable ophthalmic ointment, preferably penicillin.

CONCLUSION

1. The therapy of epiphora of the newborn is exceedingly simple if the underlying embryologic cause is borne in mind.

2. Treatment of the eye simply by ointment or lotion is of no value.

3. The condition is cured by milking the debris from the lacrimal sac by pressure of the thumb and by the use of penicillin ointment.

4. Some types of epiphora are treated by probing.

5. The obstetrician, pediatrician, or general practitioner should consider this diagnosis in any case of epiphora or crusting of the lids in the immediate postnatal period. He should employ the method outlined above in the treatment or refer the patient to an oculist because if the condition is not properly treated it may result in complications or undue anxiety on the part of the parents.

6. Treatment should be started immediately after the diagnosis is made.

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BOOK REVIEWS (Continued from Page 21)

use of penicillin. The relative values of local application of penicillin containing substances with the injection of penicillin are contrasted. Briefly the author reviews what has been learned about the antibiotic in peritonitis and several types of abscess formation. The various types of bone and joint diseases, including osteomyelitis, have been reviewed insofar as the effects of penicillin are concerned. Brief chapters consider a number of miscellaneous diseases which either respond to penicillin therapy or fail to do so, as well as its topical use in dentistry.

The third portion of the book covers other antibiotic agents. Streptomycin, the best established of these, is considered first from the viewpoint of the more fundamental knowledge as was presented in the case of penicillin and as indicated by the reviewers in the early paragraphs of this review. The clinical review covers briefly the diseases in which streptomycin has been found to be effective—in most instances those of the gram-negative bacilli. The experimental work with this drug in tuberculosis is touched upon.

In a similar fashion the author takes up the subject of tyrothricin and its topical use in certain infections. Other less common antibiotic substances are listed—substances which as yet are only in the experimental stage or have no clinical application.

For the clinician who wishes a practical review of the knowledge accumulated to date on the antibiotics this volume will be worthwhile. In the case of some diseases, the reader may wish that the author had discussed the results of treatment with antibiotics in more detail. However, the reviewer feels that the subject has been presented adequately and any criticism which might be forthcoming on the above point is more than met by the exhaustive bibliography which is cited. R. H. K.

SEX MANUAL: FOR THOSE MARRIED OR ABOUT TO BE. By G. Lombard Kelly, M.D. 84 pages, 9 illustrations. Southern Medical Supply Co., P.O. Box 1168, Augusta, Georgia. Price $1.00.

The author is an anatomist and experiential biologist in the field of endocrinology and through these has been interested in the subject of this booklet. It is written for the layman.

After presenting the need for information in sex matters, the author describes in simple fashion the anatomy of the sex organs. He compares and contrasts the psychologic and physiologic aspects of the sexual life in the sexes. Dr. Kelly presents the concept that true frigidity is a clinical rarity, being rather a reflection of ineptness or of ignorance of female physiology on the husband's part. He denies the old wives' tales relative to the menopause as related to the sex life and other matters. Contraceptives, sterility and fertility are discussed.

The reviewer feels that every physician should have something of the nature of this booklet at hand to give to prospective brides or bridegrooms and to those married individuals who have problems in this field. It is a sad commentary on our mores and the parents of our youth that they are all too often unprepared for marriage. The popular magazines are educating our women to some extent in the matters of sex life and many logically turn to their physicians for advice. In duty to his community the doctor must be prepared

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The introduction of a new procedure is usually accompanied by a period of uncertainty respecting its usefulness and value. This article provides for those not currently familiar with electroencephalography a critical and conservative analysis of its place in medical practice.

Practical Considerations of Electroencephalography For the Practitioner*

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To many physicians in general and specialized medical practice, the electroencephalograph is a confusing, complicated apparatus and the clinical value of the examination is unknown to the vast majority. Some physicians have requested occasional electroencephalograms and because it has failed to settle for them a particularly pressing diagnostic problem they have immediately discredited the examination and stamped it as a valueless procedure. However, on the opposite side are those few rare zealots who claim the electroencephalograph is a diagnostician of intracranial disorders that cannot be excelled. As is the usual case in medicine, the real truth is found somewhere between these two extremes and admittedly, in several respects, the issue is not yet settled. The newspapers and periodicals read by both lay and professional personnel have done much to distort the clinical value of the electroencephalogram.

The purpose of this discussion is to describe briefly the basic fundamentals of electroencephalography and to present concisely, according to our present knowledge and opinions, the practical clinical application of this examination.

GENERAL CONSIDERATIONS

Electroencephalography is the recording of the electrical activity of the cerebral cortex. The neurones of the cortex, as do all nerve cells, produce a recurrent transient electrical wave, which represents cellular activity or the transmission of an impulse. For some as yet unexplained reason, the cells of the brain tend to discharge or "beat" in a synchronous fashion which makes possible the recording of rhythmic cortical activity. The voltages developed are very small and when recorded from the scalp normally vary from about 5 to 100 microvolts (millionths). This is much smaller than the usual voltage of the "R" wave of an electrocardiogram which varies from 0.70 to 1.8 millivolts (thousands).

The inherent rhythm of the cortex changes with alterations in physiologic states as well as in disease. For instance, in the normal person the alkalosis produced by forced overbreathing is frequently accompanied by a slowing and an increase in voltage of the cortical waves. This is what Gibbs [1] refers to as a "build-up." Sleep produces a typical change as does psychic and physical stimulation of the subject. Drugs,[2] especially sedative and anticonvulsant medications, can greatly alter the appearance of an electroencephalogram and therefore must be taken into consideration by the interpreter, or if possible, be eliminated prior to the examination.

We believe that the clinical value of this examination is proportional to the skill of the technician and thoroughness and experience of the interpreter. There are certain minimal standards in regard to the recording of an EEG which should be insisted upon by the physician requesting the examination. It is our opinion that an acceptable electroencephalograph must faithfully reproduce cortical activity [3] and must have at least four channels. This means that there are four or more oscillographs simultaneously recording from separate areas of the brain. For routine examination eight cortical electrodes, four over each hemisphere, are the acceptable minimum (Fig. 1). The duration of recording is an extremely important factor because the patient may have abnormal brain waves which occur in bursts with intervening normal records. When such a burst of abnormal activity will appear cannot be predicted and if the record is short it is very likely to be missed. It is, therefore, felt that 20 minutes of recording time is desirable when using a six channel electroencephalograph and the time increases in proportion to a decrease in the number of channels employed.

The position of the patient during the examination, that is, whether he is sitting or lying down, is of rela-

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tively little importance. The patient should be relaxed and his eyes should be closed, but under ordinary circumstances, he should not be allowed to become drowsy as sleep is accompanied by electroencephalographic changes which are sometimes very difficult to differentiate from abnormal cortical activity. The subject should be required to hyperventilate for two or three minutes. The recording is continued during this period and also for several minutes following voluntary hyperventilation. The authors

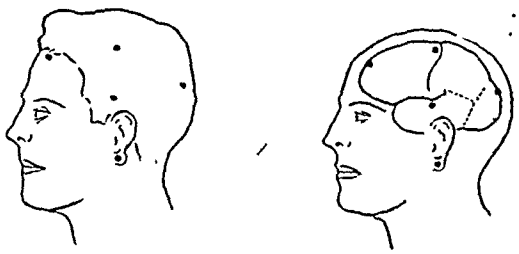


FIG. 1. Routine electrode placement includes four electrodes on each side of the head as shown above. The electrodes are referred to as frontal, parietal, occipital and temporal leads. The parietal lead rests upon parietal bone but actually records the activity of the motor cortex. An electrode is placed on each ear and is considered an "indifferent" or "ground" lead.

prefer a three-minute period of forced breathing but there are many electroencephalographers who feel that the two-minute period is adequate if co-operation is good. Hyperventilation tends to bring out latent electrical abnormalities which would otherwise pass undetected.

In order for the referring physician to appreciate the significance of the electroencephalogram report, it is wise to keep in mind the fact that the electroencephalogram of normal individuals changes according to age. A cortical pattern found in a normal child [4] would be considered definitely abnormal in an adult.[5] Similarly there are progressive changes in the brain waves as the adult advances in age.[6]

The types of cortical patterns encountered in normal and pathologic conditions have been classified differently by Gibbs and Lennox [7] and by Jasper.[8] Both these systems of classification are believed to be good and the relative advantages of one as compared to the other are not within the scope of this paper. In general we can say that normal activity (Fig. 2) can be of two types which may occur singly or in combinations. The first, Alpha rhythm, and the most common type, are waves of 8.5 to 12 per second. The second, Beta rhythm, are waves at low voltage, usually fast, which are referred to by Gibbs as "low voltage fast." Abnormalities may consist of diffuse and focal

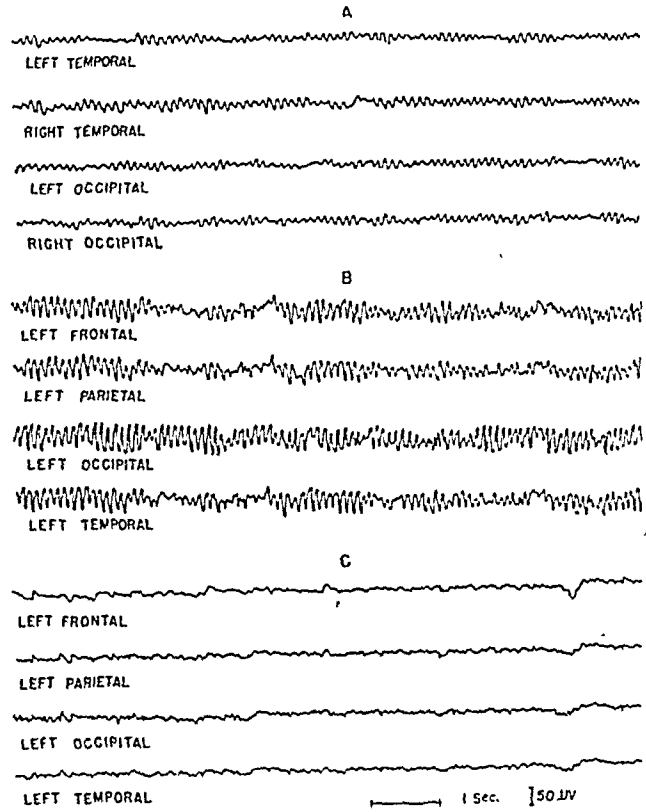


FIG. 2. Normal encephalograms. A and B are from two normal male adults with Alpha rhythm, 8.5 to 12 per second waves. C is from an adult female with normal low voltage fast activity.

dysrhythmias which in turn may be fast, slow or paroxysmal. Paroxysmal disturbances include several distinct types which are most often associated with convulsive disorders (Fig. 3). They are easily recognized by the sudden appearance of abnormal waves in a record which prior to that point was free of such activity and may have been within normal limits. Abnormalities may occur in apparently normal control subjects. The occurrence of cerebral dysrhythmia in individuals without complaints indicates a hereditary factor which is discussed later.

CLINICAL CONSIDERATIONS

The efficiency of the correlation of electroencephalographic findings with pathologic conditions has a wide range of variation. In many instances, in a specific disease the existing symptomatology and stage or rate of progression of the disease directly influence the incidence of electroencephalographic abnormalities. The effect of these variables will be considered in each of the conditions which we will discuss. There are certain mental and neurologic disorders in which the electroencephalogram is of little or no value.

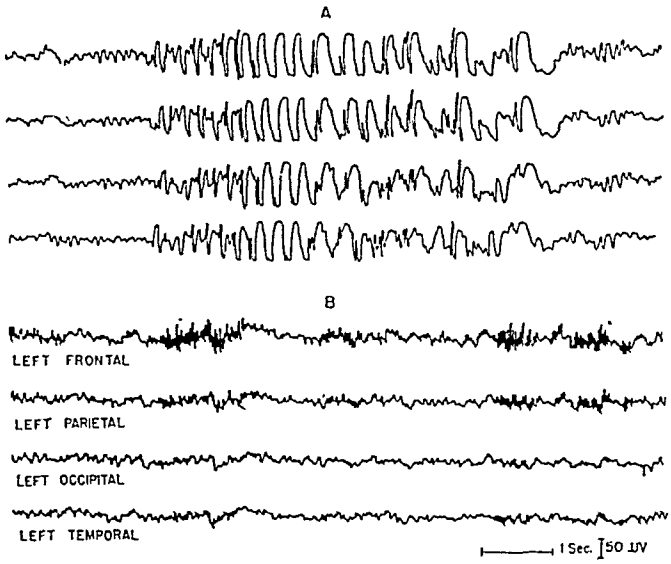


FIG. 3. Paroxysmal abnormalities in idiopathic epilepsy. A. The spike and wave typical of petit mal epilepsy. B. Paroxysmal fast activity referred to by Gibbs as the "grand mal" type of abnormality.

The more common of the disorders which are sometimes erroneously expected to be accompanied by electroencephalographic abnormalities will also be discussed.

The pathologic conditions to be included will be presented in the order of clinical importance and efficiency of electroencephalographic correlation; beginning with those in which the correlation is good and progressing to those in which the electroencephalogram is of little or no value.

EPILEPSY, IDIOPATHIC (CRYPTOGENIC)

Most investigators agree that in a series of unselected epileptics between 80 per cent and 90 per cent [7, 9, 10] will show evidence of electroencephalographic disturbance. In a series of 100 young male adult epileptics, the authors found 84 with cerebral dysrhythmia on routine examination. The examination was repeated three times and it was then found that 94 patients on one or more occasions showed disturbed electroencephalograms. These findings are in accord with Jasper who states "with repeated examination and with hyperventilation, the chances are not over 5 in 100 that a patient with a negative electroencephalogram has true epilepsy." [8] Gibbs, Gibbs and Lennox [7] in a large series of unselected epileptics found dysrhythmias in 83.7 per cent of those who were 20 years of age or over. Epileptics under 20 years had electroencephalographic changes in 91.5 per cent.

The probability of recording cortical disturbances is definitely related to the type of seizure which afflicts the patient. Individuals who suffer from petit mal seizures alone are the most apt to have abnormal electroencephalograms. Better than 90 per cent of these patients have disturbed electroencephalograms. Epileptics who manifest the condition by psychomotor seizures have disturbed electroencephalograms in approximately 85 per cent of the cases. In patients with grand mal seizures alone, the electroencephalographic efficiency is lowest—near 80 per cent. When the patient complains of grand mal seizures as well as petit mal or psychomotor attacks the likelihood of brain wave abnormalities increases and in our experience is related to the predominant type of seizure and the frequency of the attacks.

Hysterical attacks are often difficult to distinguish from true epilepsy. If the syndrome is questionable and the patient is suspected of being hysterical, a normal electroencephalogram adds strong support to that diagnosis, as from electroencephalographic evidence alone the patient has but one chance in ten that he may still be an epileptic. If the patient in question has an attack during the examination which is not accompanied by electroencephalographic abnormalities the diagnosis of hysteria is confirmed.

Electroencephalographic findings can be used as a guide in advising those who fear the appearance of idiopathic epilepsy in their progeny. It has been shown that parents and near relatives [11, 12] of epileptics have a high incidence of electroencephalographic abnormalities. We feel that the physician is justified in advising the prospective bride and groom not to marry, or a married couple not to have children if both have abnormal electroencephalograms, and one has a near relative with a history of seizures.

EPILEPSY (SYMPTOMATIC)

The differentiation of symptomatic seizures (which are the result of demonstrable cerebral lesions) from idiopathic epilepsy is important from several standpoints which include possible surgical intervention, hereditary factors and medicolegal aspects. According to Lennox [13] 7.5 per cent of all epileptics are of posttraumatic origin and are, therefore, symptomatic epileptics. Patients suffering from symptomatic seizures have a better than 90 per cent chance of having disturbed electroencephalograms. Localized cortical abnormality [14] is a common finding in symptomatic seizures (Fig. 4) and its presence makes a thorough investigation, including air studies, mandatory. In contrast, focal disturbances are uncommon in idiopathic epileptics and the spike and wave pattern (Fig. 3) is rarely, if ever, found in patients whose seizures

are the result of demonstrable focal cortical pathology. The presence of a spike and wave abnormality for all practical purposes rules out the diagnosis of symptomatic epilepsy. Penfield and Erickson [15] state "if the abnormality has the form of a 3 per second wave, or wave and spike, the possibility of eventual discovery of a focal lesion of the brain, susceptible to radical therapy, can be practically ruled out without hospitalization. If, on the other hand, the electroencephalographic study suggests a focal lesion, then admission for pneumographic study is the more desirable."

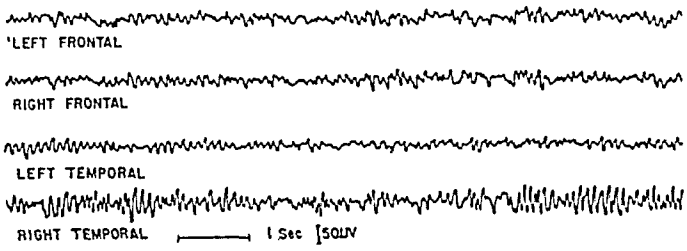


FIG. 4. Focal activity indicative of localized brain pathology in post-traumatic epilepsy. Note the difference in the abnormal pattern recorded from the right temporal lead as compared to the left temporal lead.

The medicolegal aspect of post-traumatic seizures is of increasing importance. In regard to this matter Gibbs [16] has made two very important statements: "If a paroxysmal abnormality is found three or more months after head injury, the chances are at least thirteen to one that the patient has epilepsy" and "other things being equal, if a patient has seizures and shows focal paroxysmal abnormality three or more months after head injury, the chances are three to one that he has the seizures as a result of the injury rather than as a result of the other known and unknown factors that produce seizures in an unselected group of epileptics."

Patients suspected of symptomatic epilepsy should, whenever possible, be examined after the withdrawal of anticonvulsant medication. This may require hospitalization. These drugs frequently eradicate the localized disturbance recognizable on the electroencephalogram and therefore cancel the prime purpose of the examination.

Brain Tumors

The method and value of localization of brain tumors has been discussed by numerous investigators. It is obvious that the position, rate of growth and the type of neoplasm will effect the electroencephalographic findings. Since the electroencephalogram is a record of cortical activity it follows that a tumor involving the cortex will probably be accurately localized (Fig. 5). Conversely, a deep-seated tumor will rarely be clearly localized. However, a deeply situated neoplasm will usually be accompanied by electroencephalographic changes but the dysrhythmia is apt to be diffuse.

Hoefer, Schlesinger and Pennes [17] recently presented their electroencephalographic findings in a large series of verified brain tumors. They found that "hemisphere" gliomas could be accurately localized in 72.8 per cent of cases. Another 8.1 per cent of the cases were placed under the heading of "lateralization"; these cases were verified by biopsy only and were not removed by operation. The authors state "In some of these the tumor might have been found at the site indicated by EEG if a search for it had been made." In 16.2 per cent the tumors were not localized and in 2.9 per cent they were falsely localized.

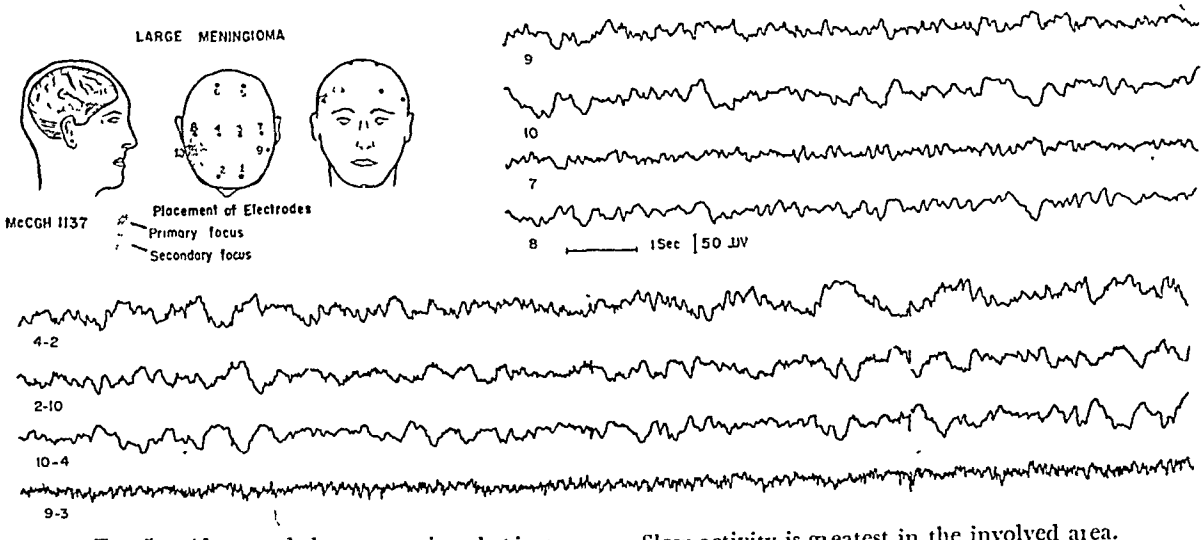


FIG. 5. Abnormal slow waves in a brain tumor. Slow activity is greatest in the involved area. An "out-of-phase" or "phase reversal" focus is present.

Meningomas in contrast to gliomas could not be localized in 22 of 77 cases. Yaeger and Luse [18] reported accuracy of localization in 77 per cent of anterior fossa tumors. It is apparent from these figures that electroencephalographic localization of brain tumors falls short of the accuracy obtained by pneumoencephalography or ventriculography. We do not feel that the electroencephalogram can be substituted for air studies but it frequently can be of clinical value and should be used as a preliminary and adjunctive examination.

Degenerative Diseases of the Brain

The authors have had an opportunity to obtain electroencephalograms from patients with the following types of rare heredodegenerative diseases: Tay-Sachs' diseases (Fig. 6) (amaurotic idiocy), Schilder's disease (encephalitis periaxialis diffuse), Heller's disease (dementia infantilis), tuberous sclerosis (Bourneville disease) and Wilson's disease (hepatolenticular degeneration). All of these patients had abnormal

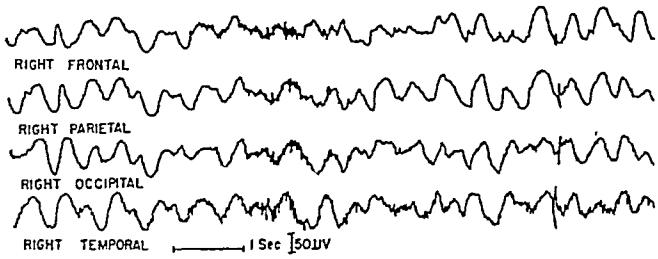


Fig. 6. Abnormal slow waves in a 17-month-old male Hebrew infant with Tay-Sach's disease.

electroencephalograms which indicated a severe cerebral disturbance. Two cases of Wilson's disease were referred to us for examination by H. R. Carter [19] and have been reported by him.

Patients suffering from multiple sclerosis will have abnormal brain waves in approximately 50 per cent of unselected cases.[20] Abnormal electroencephalograms are usually found in those individuals with multiple sclerosis who exhibit mental evidence of pathologic involvement of the brain. We have found disturbed electroencephalograms in patients prior to the appearance of mental symptomatology, but in the majority of cases the period of time was brief until clinical confirmation of brain pathology appeared. However, it is possible to find a perfectly normal electroencephalogram in spite of the obvious presence of large intracranial lesions.[21]

Encephalitis

Under this heading can be included encephalopathies which may be the result of a variety of toxins: endogenous, exogenous or bacterial. The reports of electroencephalographic studies in these patients are surprisingly meager. Our experience has been similar to that of Ross [22] who reports generalized abnormalities during the acute stage of encephalitis and meningo-encephalitis. Lindsley and Cutts [23] have observed a progressive improvement of the electroencephalogram which parallels clinical improvement and the reduction of protein in the spinal fluid. We have found that the electroencephalogram is of frequent value as a diagnostic aid in those individuals, usually children, who develop behavior disorders or mental changes which are believed to be of postencephalitic origin. Patients with mental changes due to exogenous toxins, such as carbon monoxide (Fig. 7) and lead, will also show electrical cortical disturbances.

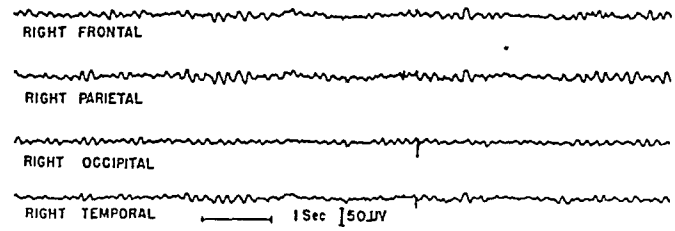


Fig. 7. Mental deterioration following carbon monoxide poisoning. Encephalogram showed diffuse cortical disturbance.

Sydenham's chorea, which according to Ford [24] is best regarded as a toxic encephalopathy, is usually accompanied by a change in the electroencephalogram. Buchanan, Walker and Case [25] stated "The irregularity is present in records from all parts of the scalp, but in patients with hemichorea the activity is usually much greater in records made from leads placed on the scalp on the side opposite the movements." Usher and Jasper [26] noted that the more severe the clinical symptoms the more pronounced were the changes in cerebral activity. In the rather small group of children with chorea we have had an opportunity to examine we are, in general, in accord with the above statements. It appears that the physician has a tool which can be used to differentiate psychogenic tics from chorea.

Head Injuries and Post-traumatic Conditions

Acute Head Injuries. If an electroencephalographic examination can be obtained within a few hours following injury it can be of diagnostic value and, in

cases in which a dispute involving workmen's compensation is anticipated, it may be of real help. Dow, Ulett and Raaf [27] have presented an excellent study of the electroencephalographic findings in 197 patients shortly after they had sustained a mild cerebral injury. Only nine of these patients had any evidence of confusion at the time of examination and none were either semicomatose or unconscious. They concluded that "if mild cerebral trauma such as we were investigating produced changes in the electroencephalographic tracing the abnormality disappeared within a period of minutes in the vast majority of the cases." Dennis Williams [28] observed in acute head injuries a definite correlation between the degree of abnormality in the electroencephalograms and the clinical state of the patient. He found that when the recent damage was sufficient to result in sensorial clouding or impaired consciousness the electroencephalogram was invariably abnormal. It therefore followers that if a patient is stuporous or definitely confused at the time of examination and has a normal record it is extremely doubtful that his condition is the result of the head trauma.

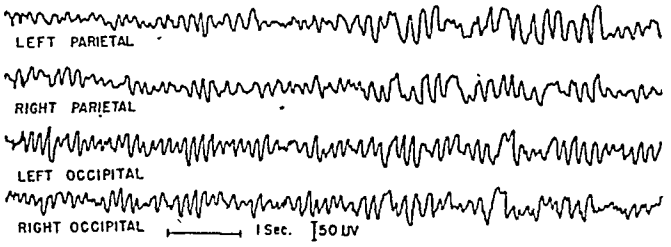


FIG. 8. Post-traumatic syndrome with slow activity appearing in all leads.

Chronic Post-traumatic States. The electroencephalogram in many post-traumatic conditions (Fig. 8) can be of value to the clinician, especially in those patients who present complaints of doubtful traumatic origin. Greenblatt,[29] Williams,[30] Heppenstall and Hill,[31] in separate studies arrived at the conclusion that approximately 50 per cent of *unselected* post-traumatic cases have abnormal electroencephalograms. These studies included patients with an extremely wide range of complaints which varied from trivial to severe.

However, Williams in breaking down his series found that the history of a simple skull fracture without dural opening did not increase the percentage of abnormality above the average for the entire series. In those patients with fracture and dural penetration, 94 per cent had abnormal electroencephalograms. One of us,[32] in a study of 116 soldiers with skull defects of traumatic origin, found that about 80 per cent had disturbed cortical rhythms. Thirteen of the soldiers miraculously escaped dural opening. This small group had a significantly lower percentage (61 per cent) of disturbed electroencephalograms.

The presence of post-traumatic headache does not increase the incidence of cortical dysrhythmia. In our series 79 per cent of those patients with headaches had disturbed electroencephalograms while 78 per cent of those without headaches had similar electroencephalographic changes. We believe this is to be expected inasmuch as post-traumatic headaches are usually the result of pathologic involvement of the cranial vascular structures [33] and have nothing to do with the non-pain-sensitive cells of the cortex whose activity is recorded by this test.

Gibbs [34] and others [35] have called attention to the fact that the incidence of abnormal electroencephalograms will decrease gradually up to two years in patients who have suffered a severe head injury but are free of symptomatic seizures. It is generally agreed that the electroencephalographic improvement parallels clinical improvement and lack of improvement is an ominous sign. If the patient suffers from post-traumatic epilepsy the electroencephalographic improvement is negligible over a comparable period of time.

In a series of 53 patients diagnosed as suffering from post-traumatic psychosis all the patients had some evidence of cortical changes by electroencephalographic examination. However, we do not feel that a normal electroencephalogram refutes a clear-cut clinical picture of a post-traumatic psychosis. Anyone with experience in the field of electroencephalography has encountered patients with obvious brain pathology who had perfectly normal records.

ALCOHOLISM

The progressive slowing which occurs with acute intoxication [36] and the alteration of cortical activity encountered in delirium tremens [37] is of interest to the investigator, but its clinical value is practically nil. However, in patients suspected of an alcoholic psychosis the presence of an organic disturbance can frequently be confirmed by electroencephalographic findings. We have found, as have Greenblatt, et al.,[38] that nearly all patients with Korsakoff's psychosis or alcoholic deterioration have abnormal brain wave records. Greenblatt found three of five patients after recovery from pathologic intoxication had abnormal electroencephalograms. We have been unable to confirm these findings in six patients, but it is obvious that the number of patients involved is far too small to make any definite conclusions justifiable. The chronic

alcoholic when not under the influence of liquor, or without evidence of mental change, shows no higher incidence of electroencephalographic disturbance than normal people. However, in those patient who have convulsive seizures which are always directly related to the consumption of alcohol a fairly high percentage will show cortical dysrhythmias which confirms the belief that these patients are truly latent epileptics.

Arteriosclerotic and Senile Psychosis

The rapidly increasing problem of mental deterioration and abnormal behavior associated with senility has been reflected in the increasing number of patients in the older age group which are examined by the electroencephalographer for his opinion as to the presence or absence of organic brain disease. We have found that about 80 per cent of patients with definite arteriosclerotic or senile mental changes have dysrhythmic electroencephalograms. Liberson and Sequin [39] have pointed out the fact that the probability of recording disturbances of the brain waves parallels certain symptoms, namely, confusion, marked irritability and emotional instability. In those patients of advanced age who are referred to us with the diagnosis of senile psychosis, paranoid type, the incidence of electroencephalographic disturbance is much less (20 to 25 per cent). This suggests to us the possibility that in at least some cases the conclusion that the illness is of organic etiology is a false assumption, or the organic changes are mild and only partly responsible.

Central Nervous System Syphilis

In a group of unselected cases of central nervous system syphilis, approximately 50 per cent will show evidence of cerebral disturbance by electroencephalographic examination. As a rule, the electroencephalograph parallels the severity of the infection as manifested by the clinical picture. Normal electroencephalograms usually occur in those patients with little or no clinical evidence of cerebral involvement. Both slow and fast abnormality which may be paroxysmal are encountered but slow waves are the most frequent. Greenblatt and Levin,[40] in a careful review, reported that 91 per cent of patients with general paresis and seizures had abnormal EEG's. In those paretics without seizures only 44 per cent had abnormal EEG's. In patients with meningovascular lues (Fig. 9) without seizures, the incidence of brain wave disturbance is 44 per cent. If seizures are present the incidence is 89 per cent. In patients with pure tabes only 14 per cent have disturbed brain waves. A patient receiving antiluetic therapy who has a disturbed electroencephalogram frequently will show improvement in his tracing. This is especially true in those patients who have received penicillin therapy.[41]

Narcolepsy

The electroencephalogram of a narcoleptic is only of value when the patient has an attack of uncontrollable sleep during the examination. In our experience the "interseizure record" of the narcoleptic fails to show the types of typical paroxysmal activities

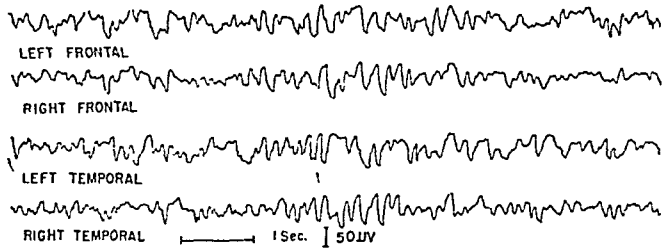


Fig. 9. Meningovascular lues in a 38-year-old white male, encephalogram shows irregular abnormal slow waves.

encountered in the epileptic. This has been previously pointed out by Dynes and Finley.[42] Cohn and Cruvant [43] claim that narcolepsy and epilepsy are electroencephalographically similar. We are in obvious disagreement with them and we are, in addition, skeptical of Wilson's concept that these two syndromes are etiologically similar. A series of patients suffering from uncontrollable sleep will show, in about one out of five cases, electroencephalograms with continuous slow activity. This finding is of little value as it is a nonspecific abnormality but suggests to us that these patients with slow waves are in some way different from the others.

However, when a narcoleptic has a spell of uncontrollable sleep during the recording of the electroencephalogram, there is a precipitous onset of sleep waves.[44] This sudden change in the record is characteristic of narcoleptic sleep, and is not duplicated in normal persons who become drowsy or go to sleep during the examination. The clinical value of the electroencephalogram in those suspected of narcolepsy, therefore, largely rests upon the chance of the patient having a spell during the examination. An interseizure record with the spike and wave of petit mal would support the diagnosis of epilepsy rather than narcolepsy, and the therapeutic program would have to be planned accordingly.

Syncope

Under this heading fall several types of attacks which are characterized by brief periods of unconsciousness and which may be referred to by the pa-

tient as "fainting spells" or "blackout spells." The so-called dizzy spells which are a concomitant or related complaint will also be included here. These oft-encountered complaints may be a real challenge to the diagnostic and therapeutic skill of the physician.

In general we agree with Levin, Katz and Greenblatt [45] who have expressed the belief that in patients with "fainting" or "dizzy spells" the *interseizure* electroencephalograms are essentially the same as those encountered in a group of normal individuals. They eliminated any patient with epileptoid manifestations such as a preceding sensory aura, muscle rigidity or clonic muscular movement during the attack, tongue biting, etc. Such attacks should rightly be classified as minor seizures, petit mal or some other form of epilepsy. These patients, as would be expected, have a high percentage of electroencephalographic abnormalities. Some patients complain of "fainting spells" which, from the available but perhaps not accurate history, are not accompanied by suggestive epileptic manifestations, yet have typical electrical disturbances and respond to anticonvulsive medication.

If by chance or intention the patient has a "fainting spell" during the examination the electroencephalogram can be very revealing. In patients who suffer from true carotid sinus syncope or vasodepressor fainting, the period of unconsciousness is accompanied by electroencephalographic changes, that is, diffuse slow waves. These two types of syncope, as demonstrated by Engel and Romano,[46, 47] can often be precipitated by the appropriate noxious stimulus. However, if the patient is suffering a hysterical conversion the pattern remains unchanged. We, as have others,[48] have encountered patients who seemingly faint when pressure is applied to the area of the carotid sinus but the electroencephalogram remains unchanged. Some investigators explain this as the cerebral type of carotid sinus syncope. However, it is our belief that these patients are psychoneurotics and in one patient who was very suggestible we were able to produce syncope by stimulation in unrelated areas of the body.

Psychopathic Personality (Including Homosexuality)

Several investigators have reported a high percentage of electroencephalographic abnormalities in persons believed to be "psychopathic personalities." [49-52] Some of these authors express the opinion that the behavior of these maladjusted individuals is governed or influenced by their pathologically functioning brains. However, we have been unable to confirm these findings and we are in agreement with Simon, O'Leary and Ryan [53] who report only a slightly higher incidence of electroencephalographic abnormality in a series of psychopaths as compared to that in a normal control group. When a dysrhythmic recording is obtained in a personality disorder it suggests to us a faulty diagnosis, and the possibility of organic brain disease or epilepsy must be considered as a cause of the patient's difficulty. The possibility of epileptic conditions distorting the findings has been pointed out by Gibbs [54] who states "only endless confusion will result if the original diagnosis is retained in spite of the finding of significant electroencephalographic abnormality and in the face of a good response to anti-epileptic medication."

It is our feeling that an electroencephalogram can be of value in patients believed to be psychopathic personalities, not as a diagnostic aid for that diagnosis, but to rule out the possibility of organic brain disease or epilepsy as the etiologic basis or contributing factor which manifests itself as a personality disorder.

Migraine

The electroencephalogram of a patient complaining of classical migraine is not only usually normal when the patient is free of headache, but is also normal during severe headache.[55, 56] Engel, Ferris, and Romano [57] have shown that patients with migraine have a peculiar electroencephalographic disturbance when experiencing scotomas. This disturbance is a focal electrical abnormality which appears in one occipital leap, while the cortical activity remains normal in all other cortical leads. To obtain a tracing at the proper time is a definite problem, and although this is an interesting and important observation, we do not feel it is of clinical use at the present time.

Many patients referred to the Electroencephalograph Laboratory have a questionable diagnosis of migraine. These patients do complain of severe headache but their accompanying and additional symptoms or complaints vary widely. Such patients will occasionally show electroencephalographic disturbances which point to definite brain pathology. However, if the patient is neurologically negative, has a questionable history, and in addition, has a negative electroencephalogram, the clinician will rest easier and should investigate the possibility of a functional etiologic factor.

Psychoneurosis, Schizophrenia and Manic-Depressive Psychosis

The electroencephalograph at present has no practical importance to the practitioner who is concerned with a psychoneurotic, schizophrenic or a manic-

depressive patient. The electrical cortical activity, in general, in these patients falls within normal limits. Many investigators have found variations in electroencephalographic patterns which they feel are more frequent in certain types of major or minor mental disorders. However, these variations are not consistently present, they are not considered definitely abnormal, and they are at present of no diagnostic or prognostic value. Some of these investigations are of interest and may eventually end in usefulness. Many electroencephalographers have noted that very tense, anxious individuals will have an electroencephalogram characterized by a large amount of "low voltage fast" activity. Davis [58] reported that this type of activity was frequent in schizophrenics, but it is also found in apparently normal individuals and is considered to represent a type of normal adult activity. The presence of this type of normal activity seems to reflect the emotional state of the patient.

COMMENT

This paper is not meant to be a complete review of all the disorders in which disturbed electroencephalograms have been reported. Rather, it is meant as a guide for the practitioner so that he can more intelligently use this examination for the benefit of his patient. We wish to reiterate that in a few instances our opinions are divergent from those of other workers in this field, and it is conceivable that with future investigation and experience we will alter our opinions on certain of the questionable subjects.

SUMMARY

The basic fundamentals of electroencephalography have been reviewed. The clinical value of this examination was discussed as related to the following pathologic conditions:

1. Idiopathic epilepsy
2. Symptomatic epilepsy
3. Brain tumors
4. Degenerative diseases of the brain
5. Encephalitis
6. Head injuries and post-traumatic conditions
7. Alcoholic psychosis—acute alcoholism
8. Arteriosclerotic and senile psychosis
9. Central nervous system syphilis
10. Narcolepsy
11. Syncope
12. Psychopathic personality
13. Migraine
14. Psychoneurosis
15. Schizophrenia
16. Manic-depressive psychosis

It is concluded that the electroencephalogram is frequently of value in the first nine conditions, it is occasionally of value in narcolepsy and syncope and rarely, if ever, of value in the last five diseases.

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Poliomyelitis apparently occurs rarely in the pregnant woman. The effect of its appearance under these circumstances is considered.

Poliomyelitis and Pregnancy

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In the 1946 outbreak of poliomyelitis in north eastern Ohio, 251 patients, 5 of whom were pregnant women, were reported up to September 30th on the service of Dr. John A. Toomey.

This induced me to review the literature on the relationship between pregnancy and poliomyelitis. Aycock [1] states that the normal expectancy is less than one pregnant woman in 1,000 cases of infantile paralysis, or less than one case of poliomyelitis in 50,000 pregnancies. Instead of the expected incidence of 0.2 per cent, our percentage has been 2.3 per cent or 11.5 times higher. Brahdy and Lenarsky,[2] found three pregnant women in 1,010 cases in 1931; in 1939, four cases were found in Detroit, in a total of 528 patients. Recently Hortsmann, Ipsen and Lassen,[3] in Copenhagen, found 20 pregnant women between the ages of 20 and 34 years among 62 patients with the disease.

It may be that pregnancy predisposes to poliomyelitis; on the other hand, it still remains true that the majority of reports of pregnant women suffering from poliomyelitis have been in the form of isolated cases, and sometimes without any relation to the total number of cases in the corresponding epidemics. This makes it difficult to reach a conclusion. The Danish authors mentioned previously consider that it is possible that the increase in the age incidence during recent years toward the adult stage has tended to disclose this characteristic of the disease—an otherwise previously hidden susceptibility.

Some investigators think that an endocrine factor diminishes the incidence of poliomyelitis in early pregnancy. Peelen [4] states that in 60 cases 19 per cent had poliomyelitis in the first trimester of pregnancy, 26 per cent in the second, and 55 per cent in the last. Weaver and Steiner [5] found similar results working experimentally with cotton rats. The five cases recorded last year in the City Hospital were all in the first trimester of pregnancy, contrary to the above dictum. Our number of cases is too small, however, from which to draw any conclusion.

All reports agree that an acute attack of poliomyelitis does not interfere with the course of pregnancy, each condition following its own evolution independently, and that a normal labor should be expected. An acute attack of poliomyelitis *is not an indication for interruption of pregnancy.* The only exception in pregnancy is when the disease occurs in the last trimester and respiration becomes difficult, then a cesarean section may be done for delivery.

The incidence in complications, spontaneous abortions, cystitis, etc., is identical with that incidence which occurs in normal women with no variations attributable to the disease. In our series there were three abortions and one threatened abortion in a patient who previous to the onset of the disease had attempted some interference. While the incidence of abortion in this series is high it might be that the treatment for poliomyelitis, which included brisk and frequent catharsis, could have initiated the condition.

Transmission of the virus through the placenta has not been shown. This is similar to Netter's (1911) finding in human rabies in which intra-uterine transmission never occurs.

Poliomyelitis does not influence the course of pregnancy following the acute attack of the disease, and there are reports of women who became pregnant three months after the onset of the disease. In a long-standing paralysis with marked malformations of the bones, one may expect harmful effects during labor and in this instance a cesarean may be done.

SUMMARY

1. It is questionable whether pregnancy plays any part in susceptibility or resistance to the virus of poliomyelitis.

2. An acute attack of the disease does not affect the course of normal pregnancy.

3. Acute poliomyelitis does not interfere with labor, except in cases in which respiratory involvement occurs or when the abdominal muscles are so weak that propulsive movements are not possible during labor.

4. There is evidence that the fetus remains undamaged while the mother has acute poliomyelitis.

5. No proved case of congenital poliomyelitis has been reported.

6. Poliomyelitis, per se, does not affect future preg-

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nancies except in those patients with marked malformations of the pelvis which may occur as a result of this disease.

7. Poliomyelitis is not affected by early pregnancy. In late pregnancy poliomyelitis may aggravate the condition of a patient with respiratory involvement. It may also be complicated by severe cystitis.

8. In our series of five pregnancies associated with poliomyelitis there were three spontaneous abortions and one threatened abortion following an attempted interference. It is difficult to determine whether these three abortions were related to the concurrent poliomyelitis or whether they were due to other causes.

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BOOK REVIEWS (Continued from Page 26)

to advise and may turn many a marriage from a boring to an interesting experience and in turn have an effect on the incidence of divorce. Dr. Kelly's booklet can be an aid to the physician in instructing liis patients.

This booklet is sold only to physicians and medical bookstores so that it may be distributed by the doctor himself or on his prescription. Incidentally, it is of interest that several medical schools are making provision for senior students to obtain copies. For too many generations of medical students teaching in these matters has been inadequate.

R. H. K.

REHABILITATION THROUGH BETTER NUTRITION. By Tom D. Spies, M.D. 94 pages and 50 illustrations. Philadelphia, Saunders, 1947.

The author of this monograph terms it "an exposition of practical therapeutics" with the assigned purpose of calling attention to the fact that individuals debilitated solely by nutritional deficiencies gain strength promptly following specific nutritive therapy. It would be surprising if anyone would disagree with this thesis which has previously been so well established, especially by the earlier workers in nutrition such as Goldberger.

The book cannot serve as a complete guide to the understanding or treatment of nutritional disorders. In common with much current nutritional thought, the book concerns itself chiefly with vitamins. The discussion includes vitamin A deficiency, pellagra, thiamine and riboflavin deficiency, vitamin C deficiency and, all too briefly, protein deficiency. Sketchy accounts of the clinical characteristics of the anemias are included. Deficiencies of vitamin K and D are omitted and nothing is said concerning deficiencies of many of the common inorganic substances, such as iodine deficiency. Caloric overnutrition, or obesity, is inadequately discussed. Therapeutic management of iron deficiency anemia and of pernicious anemia appears to have been ignored. The reader is not left with a clear concept of the therapy of sprue and nutritional macrocytic anemia. Discussion of folic acid is omitted entirely. Some of the 27 photographs are good, others are disappointingly poor.

There are certain inconsistences. Thus, on page 31, it is recommended that patients with thiamine deficiency be treated with 10 to 50 mg. of the vitamin parenterally and, on page 38, the same mode of administration of vitamin C is recommended, although the author concludes with the principle that patients should be given vitamins by mouth (page 83). On page 43, the marrow of the patient with hypochromic macrocytic iron deficiency anemia is erroneously stated to be characterized by an increased number of megaloblasts. On page 12, it is mistakenly stated that physical exercise increases the requirement of all the nutrients.

The book is concluded by a listing of 124 publications by Doctor Spies since 1931. No other bibliography is included and direct connection between text and bibliography is lacking. This book would appear to be of limited usefulness.

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Critique on Diagnosis and Treatment of Cortical Adrenal Disease *

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INTRODUCTION

There are conflicting views regarding the physiologic significance of the adrenal glands and their relation to disease of these glands and to various other diseases. Those views have an important bearing upon the diagnosis and treatment of adrenal cortical disease, especially. The present author believes that certain diagnostic procedures that are frequently employed and the practice of administering synthetic steroid products (desoxycorticosterone acetate) are unsafe and cannot be justified by tenable scientific information.

Admittedly, some of the criticisms which will be presented here may be susceptible to challenge by proponents of opposite convictions. However, they have their origin in the results of original experimental investigations and clinical observations conducted during more than 30 years. It seems, therefore, that if they are not deemed entirely valid they may, at least, provoke serious thought or, indeed, greater caution in regard to certain accepted diagnostic and therapeutic practices. A critical evaluation of some of the prevailing views and their fundamental bases should serve a useful purpose.

Significant information concerning the physiology and pathology of the adrenal glands often appears to be overlooked or ignored. Concepts exist which, on dubious premises, relate certain diagnostic and therapeutic procedures to unproved physiologic assumptions regarding adrenal dysfunction. Indeed, there are indications that not every author has distinguished clearly between the adrenal cortex and the medulla in relating the gland to etiology, diagnosis and treatment of disease. Nor is there always concern whether a supposed relation of the adrenals to a particular disease is in the nature of excessive or of deficient function. Thus, it is found in medical literature that Basedow's disease (or hyperthyroidism) is alleged to be benefited by surgical *reduction* of adrenal cortical function; on the other hand the same therapeutic claim is made for *increasing* the availability of adrenal cortical activity by the administration of an adrenal extract.

The number and variety of diseases in which, by assumption or implication, the adrenal glands are alleged to play a significant etiologic role is amazing. For example, surgical or x-ray interference with adrenal function has been employed for the following conditions: Buerger's, Basedow's, Cushing's and Raynaud's diseases, diabetes mellitus, arterial hypertension, spontaneous gangrene, epilepsy, peptic ulcer, and even "constipation and indigestion." It should be obvious that one particular gland can hardly be responsible for so many different ailments.

At present, it does not seem proper to attribute physiologic abnormality or pathologic alteration of the adrenals to known diseases other than Addison's disease, certain tumors of the adrenal cortex and pheochrome tumor of the medulla. We may include, also, certain diseases of other endocrine organs, in which the adrenal glands appear to participate in the development of the syndrome as a whole.

We believe that intervention at the adrenal glands, by surgical procedures or by irradiation as a supposed therapeutic measure for the treatment of hypertension, diabetes, and various other diseases, is an unwarranted risk to human life and health. It cannot be justified by substantial scientific evidence of adrenal involvement except, as mentioned, in cases of malignant tumors of the gland. Partial adrenalectomy or attempts to denervate the adrenals can easily lead to vascular damage and degeneration of the adrenal cortex with consequent development of Addison's disease resulting in death.[1, 2]

Insofar as the secretion of epinephrine (adrenalin) from the adrenal medulla is supposedly concerned with the etiology and pathologic physiology of diabetes or of hypertension, there is ample experimental evidence to contradict this view.[3-5] The possibility of an increased epinephremia can be supported only in the case of paroxysmal hypertension associated with the existence of a pheochromocytoma of the adrenal medulla. Even in this case the actual detection of epinephrine in excess in the blood has not been accomplished.

Epinephrine secretion from the adrenal medulla

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Supported by the G. N. Stewart Memorial Fund, aided by grants from the Sarah Mellon Scaife and the Renziehausen Foundations.

is not indispensable for life and good health.[6] It obviously is not an important factor in the causation of the above-mentioned diseases in which treatment has been attempted by adrenal reduction or denervation. The indispensable function of the adrenal glands is performed by the internal secretion of the cortex (interrenal gland tissue). Therefore, we shall limit our discussion to diagnosis and treatment of adrenal cortical disease.

Within the past 20 years conflicting ideas have arisen concerning the diagnosis and treatment of adrenal cortical (interrenal glandular) insufficiency, particularly Addison's disease. On the basis of his own physiologic investigations and clinical experience, the present author is unable to agree with a number of ideas which have been proposed by others and have received widespread acceptance.

For example, it can be questioned whether it is proper, or even useful, to precipitate a crisis in order to recognize the presence of Addison's disease. On the basis of clinical and experimental experience with Addison's disease such a procedure can be condemned as not only dangerous but unnecessary for arriving at a reasonably certain diagnosis. Nor does it seem possible to defend the practice of administration of a toxic steroid compound, viz., desoxycorticosterone acetate, as a therapeutic agent, in view of its known pharmacodynamic potentialities. Procedures which endanger the patient's life cannot be justified by substantial facts in adrenal physiology and pathology.

The essential points for our discussion can be elaborated most effectively by brief presentation of some important data on the physiology and pathology of the adrenal cortex, with emphasis on their clinical significance.

NORMAL AND PATHOLOGIC PHYSIOLOGY OF THE ADRENAL CORTEX (INTERRENAL GLAND)

In any consideration of the adrenal glands in relation to disease, it must be realized that the adrenal is composed of two distinctly different endocrine structures which, in higher animals, are united anatomically into one gland. This anatomic fact does not relate them functionally, i.e., as one organ, any more than is the case with the thyroid and parathyroid glands or the insular and acinar tissues of the pancreas. Physiologically, as well as morphologically and histogenetically, the component parts of the adrenal gland, the cortex and medulla, are different and independent endocrine structures. In certain lower animals they exist as such, being separated anatomically as the interrenal gland (cortex) and the chromaffin bodies (medulla).

The adrenal cortex or interrenal gland is derived from the mesoderm while the medulla or chromaffin tissue is ectodermal in origin. Normal function of the adrenal cortical hormone (interrenalin) is indispensable for life and health; that of the hormone of the medulla (epinephrine) can be suppressed completely without inducing any detectable ill-effects. Thus, insofar as existing substantial evidence permits us to relate the adrenal glands to disease, the cortex and not the medulla must be considered as the important factor.

Epinephrine secretion from the adrenal medulla can be abolished experimentally in laboratory animals. In some animals there is a high incidence of accessory cortical bodies; in these the main adrenals can be completely removed (cortex and medulla). The accessory bodies, consisting of cortical cells only, suffice to support life and good health of the animals. In other species, epinephrine secretion is abolished by excision of one adrenal and complete denervation of the other gland. Assay of blood collected from that remaining denervated gland has demonstrated complete abolition of epinephrine secretion. Yet, such animals have been observed over periods ranging up to one and one-half to two years and have shown no detectable signs of ill health or disturbance of essential, normal functions.[6] Only when all or a major portion of the remaining cortex was excised did the animals develop manifestations of adrenal insufficiency.

Animal species in which there is a high incidence of accessory adrenal cortical tissue, e.g., rats, rabbits, are unsuitable for studies on adrenal insufficiency since a very large proportion of them can survive the excision of both adrenals, the accessories being capable of providing for the essential function. Only a very small amount of healthy adrenal cortical tissue suffices to sustain life and health. It has been estimated that less than one per cent of the total amount of adrenal cortex existing normally can maintain normal function if it possesses an adequate blood supply.[2] Nevertheless, much of the recent investigation on adrenal insufficiency consists of experiments with adrenalectomized rats.

Indispensability of Adrenal Cortical Function. Experimental excision of both adrenals in animals that do not possess accessory cortical tissue invariably leads to death within a very short time, usually in one to two weeks if the glands are completely removed.[7] As is the case in the human being having severe disease of the adrenals (i.e., Addison's disease), experimental

production of extensive degeneration of the adrenal cortex, although the medulla remains intact, is followed by a fatal outcome but after a longer interval unless adequate regeneration of cortical cells takes place.[2] This is additional proof that Addison's disease results from pathologic alteration of the adrenal cortex and not of the medulla as was supposed until quite recently.

Function of the Adrenal Cortex (Interrenal Gland). The function of the adrenal cortex, or interrenal gland, is indispensable for life and health. The physiologic disturbance and fatal outcome of complete adrenalectomy, subacute or chronic adrenal cortical degeneration, or Addison's disease are the outcome of loss of function of the indispensable adrenal hormone, interrenalin. The results of adrenalectomy and of clinical or experimental degeneration of the adrenal cortex constitute evidence that the interrenal glandular cells elaborate and secret an indispensable hormone. This is further demonstrated by the beneficial effects of administration of the hormone-containing extract of adrenal cortex (substitution therapy).

In the original experimental investigations by Rogoff and Stewart[7] the name "interrenalin" was proposed for the hormone of the adrenal cortex, since it is derived from the *interrenal* gland tissue. Some writers employ the name "cortin." This is a physiologic and etymologic misnomer and has been pretempted for designation of a commercial product of unknown merit. It, therefore, should not be employed in scientific literature.

An idea has been disseminated that *there is no such thing as an adrenal cortical hormone but, rather, numerous hormones each of which has a special function, the sum of them all representing the function of the adrenal cortex.*[8, 11] This view is based on the fact that a number of crystalline steroid compounds have been extracted from the adrenal cortex. Some of these compounds also have been prepared synthetically. Administration of various of the compounds was found to yield effects which have been interpreted in terms of specific adrenal functions. As will be shown in the discussion which follows, such interpretations can be easily controverted and may, therefore, be quite misleading.

It has been alleged that the principal functions of the adrenal cortex are to regulate (1) carbohydrate metabolism, and (2) water balance, renal function, and electrolyte balance in the blood, particularly of sodium and potassium ions. These views are based largely or entirely upon the effects of administration of some of the steroid products derived from the adrenals. employing normal and adrenalectomized animals, chiefly rats. It should be emphasized again that adrenalectomized rats or rabbits, in general, cannot yield reliable information regarding adrenal insufficiency, since a very large proportion of these animals possess accessory adrenal cortical bodies.

The dosage of the crystallizable steroids or their derivatives employed in those observations may be classed as pharmacologic or toxic and not physiologic. It is not known if there is such a thing as physiologic dosage of these steroids, for it has not been demonstrated that any of them actually are secreted by the adrenal glands.

Although those steroids are derived from adrenal gland tissue and, possibly, one or more of them might participate in the elaboration of the adrenal cortical hormone, interrenalin, or else might be related to some function or functions other than the maintenance of life, e.g., the functional interrelationship with the sex glands, they are not themselves the hormone or hormones which attribute to the adrenal cortex its *indispensable* function.

The idea that the "prepotent function" of the adrenal cortex is concerned with the regulation of carbohydrate metabolism has received considerable notice. This view is based on certain experimental observations in which a decided hypoglycemia resulted from bilateral adrenalectomy,[9] and other experimental observations which support the view that the liver fails to store glycogen in animals that have been deprived of the adrenals.

It should be realized that adrenalectomy is a serious physiologic as well as surgical procedure. Many of the observations on adrenalectomized animals that are reported in the literature can be attributed to results of inadequate surgery rather than, or in addition to, physiologic consequences of the loss of the adrenal glands. It has been demonstrated that, in dogs, cats, rats and rabbits, if the animals recover properly from the surgical operation and eat well, the liver stores glycogen in normal amounts and there is a normal level of blood sugar after bilateral adrenalectomy.[10, 12] Often, the level of blood sugar is found at the lower limit of the normal range, if at all reduced, in adrenalectomized dogs and cats and in Addison's disease.

The other views, mentioned above, concerning adrenal cortical function, are based on certain phases of the physiologic disturbance that occurs in adrenalectomized animals and on pharmacologic reactions elicited by administration of some adrenal steroids. The physiologic disturbances can be explained as various phenomena which result from adrenal insufficiency rather than each one of them representing a disturbance of a specific function due to loss of one of nu-

merous specific hormones. This is supported by the following observations.

When all of the crystallizable steroids which are alleged to be specific adrenal hormones are removed from a potent, hormone-containing adrenal cortical extract, an amorphous fraction remains. *That fraction is fully active in preserving life and health in completely adrenalectomized animals.*[11] This cannot be said about any one of the alleged "steroid hormones," nor of combinations of some or all of them.

Nearly 25 years ago, Rogoff and Stewart [7] suggested that the indispensable function of the adrenal cortex is in the nature of an essential complex metabolic regulation. Other important though not indispensable functions also may be performed, e.g., an interrelated function with the gonads and with other endocrine glands. At present, it does not seem that this original concept of adrenal cortical function can be discarded in favor of any of the other proposed views. This can be supported by a critical evaluation of available experimental and clinical evidence.

Pathologic Physiology. It was demonstrated that the loss of adrenal cortical function resulting from complete bilateral adrenalectomy, in dogs and cats, is followed by evidence of the development of an acute profound intoxication, indicating a severe complex metabolic disturbance. The principal manifestations of adrenal cortical insufficiency are gastro-intestinal derangements, blood chemical changes, muscular asthenia and disturbances in the circulatory and nervous systems.

In general, the same phenomena occur, but are less severe than in adrenalectomized animals and develop more gradually, in the subacute or chronic states of adrenal insufficiency seen in Addison's disease and in experimental animals with subacute and chronic degeneration of the adrenal cortex.[2]

The most common and characteristic change which has been found to occur in the blood is an elevation of the total NPN. This is due to an increase in the so-called "undetermined fraction" of the NPN. The urea nitrogen also increases but this is not sufficient to account for the elevation of the total NPN; nor do any changes in the other components of the total NPN account for the elevation since they usually are not altered significantly.[12]

A reduction in the level of sodium chloride in the blood was found in most but not in all adrenalectomized dogs.[12] Loeb et al.[13] observed that a reduction of NaCl in the blood is associated with an increased elimination of sodium by the kidneys. Although this has been accepted, widely, as characteristic evidence of adrenal cortical insufficiency, its importance as a pathognomonic phenomenon appears to have been exaggerated. For, it has been observed that the level of sodium chloride in the blood may be normal at a time when definite evidence of adrenal insufficiency exists, in a significant proportion of adrenalectomized dogs,[12] and also in clinical and experimental Addison's disease.[2]

Retention of potassium in the circulation also is supposed to be a pathognomonic occurrence in adrenal insufficiency. This requires the support of more conclusive evidence. Microchemical methods for the determination of potassium in blood are none too satisfactory or reliable. Even in cases where the chemical determinations may be deemed satisfactory the increased amounts of potassium can represent a relative change in concentration corresponding with a degree of hemoconcentration which is frequently present in acute adrenal insufficiency.

The fact that administration of potassium salts, or withholding salt from the diet, result in aggravation of symptoms in adrenal insufficiency or Addison's disease is not, in itself, enough to support the view that the physiologic disturbance in those conditions represent a specific alteration in the sodium-potassium balance in the blood. The toxic action of potassium salts, in a pathologic organism, can as well or better be explained as a pharmacodynamic effect. Likewise, salt deprivation, superimposed upon an already existing severe complex metabolic derangement, could be expected to aggravate the physiologic disturbance. In neither case does the fact substantially prove specific regulation of function of sodium or potassium by the adrenals.

The physiologic alterations which ensue in consequence of the loss of adrenal cortical function are so profound that any or all of the aforementioned blood changes can occur as part or parts of the whole process, as the result of a more fundamental complex derangement in the organism. Certainly, it does not seem entirely satisfactory to single out any particular one of those changes as the primary disturbance which results from loss of the function of the adrenal cortical hormone. Nor is there substantial evidence that each one or more of the changes represents a disturbance or disturbances specifically referable to loss of a particular one or another of the supposed multiplicity of hormones that have been alleged to represent adrenal cortical function. If pharmacologic effects of the adrenal steroids are to be related to adrenal function, much more tenable evidence of their actual normal secretion, in physiologic amounts, will have to be established by unequivocal experiments.

DIAGNOSIS OF ADRENAL CORTICAL INSUFFICIENCY

There are but little if any important differences in opinions regarding diagnosis of hyperfunctional adrenal cortical diseases such as are associated with tumor or hyperplasia. However, the controversial aspects of adrenal cortical physiology introduce important differences concerning the basis for diagnosis and treatment of adrenal insufficiency, or hypofunction.

The term "hypoadrenia" (or hypoadrenalism) frequently is employed in clinical literature although often there is doubt in the mind of the reader whether the author intends to refer to functional deficiency of the cortex or the medulla. If the latter, it is evidence of failure to recognize that function of the medulla (epinephrine secretion) can be abolished without causing ill effects; if reference is to the cortex, it is often little else that a presumption based on the presence of one or more symptoms which may occur in but are not necessarily pathognomonic of adrenal cortical insufficiency.

Genuine, unquestionable adrenal cortical insufficiency can be recognized only in unmistakable cases of Addison's disease or in cases where definite symptoms of adrenal insufficiency follow surgical interference with the glands as therapeutic procedures. In Addison's disease there usually is little if any difficulty in arriving at a diagnosis by one who has had adequate experience with the disease. The history of progressive muscular and circulatory asthenia, generally associated with a characteristic pigment deposition in the skin and mucous membranes, gastro-intestinal derangements which become frequent and increasingly aggravating, all of which originally were described by Addison, suggest the diagnosis.

Often there have been one or two acute or subacute exacerbations by the time the condition is recognized clinically. If, during such an exacerbation, the blood chemical changes which have been mentioned previously are found, the diagnosis of Addison's disease can be made with reasonable certainty. The author has described a valuable diagnostic sign, the "costo-lumbar index," which is helpful. He also has called attention to the existence of an aversion to fatty foods, in most cases.[14, 15]

The one clinical symptom that generally has been relied upon most for the diagnosis of Addison's disease is the presence of pigmentation. This can be and often has been misleading. Not only does pigmentation occur in a number of other conditions which are not associated with extensive degeneration of the adrenal cortex, but Addison's disease may exist in severe form with little or no pigmentation. Indeed, this has been observed and reported by the author as occurring commonly in blonde individuals, in whom the diagnosis of Addison's disease was confirmed at autopsy.[14, 15]

Recent literature stresses the importance of sodium and potassium determinations in the blood for the diagnosis of Addison's disease. Some clinicians actually rely upon the evidence thus obtained to arrive at a diagnosis of *functional* adrenal insufficiency, not necessarily involving pathologic alteration of the adrenal glands. Although changes in the concentration of sodium and potassium salts in the blood have been found during acute crises of Addison's disease they are often absent, especially during remissions. Nor does the presence of such changes positively indicate only adrenal insufficiency since they occur in some other conditions as well. Furthermore, as already pointed out, the level of sodium chloride in the blood frequently is found to be within the normal range in completely adrenalectomized animals.

On the basis of the alleged specific relationship of the Na-K balance to adrenal cortical function, some clinicians have resorted to the practice of precipitating a crisis as an aid in the diagnosis of Addison's disease. This can be accomplished by depriving the patient of salt or by the administration of toxic amounts of potassium compounds. It is not surprising that an individual already afflicted with a severe complex metabolic disturbance will react to such further handicaps by developing an acute exacerbation of the disease. Such extremely dangerous procedures are unwarranted and cannot be justified by substantial facts derived from clinical experience or experimental evidence. It is not necessary to risk the life of a patient by precipitating a crisis in order to arrive at a diagnosis of Addison's disease.

Other diagnostic tests, e.g., the so-called water tests, have been proposed but have not proved to be reliable. Any test that is based on the assumption that one or another of the phenomena which occur in adrenal insufficiency is pathognomonic can only be misleading. In general, they also occur in various other conditions, and the test is often positive in some conditions that are not related to adrenal disease. In case of doubt, it seems much better to risk error, on the safe side, and to rely upon confirmation of the diagnosis by seeking to obtain favorable therapeutic results from administration of a properly tested potent adrenal cortical extract. This, at least, can do no harm.

In most cases, one generally can rely upon the following criteria for diagnosis of degenerative disease of the adrenal cortex (Addison's disease). History of progressive and profound muscular weakness, associated with development of pigment in the skin and mucous membranes (except, as mentioned, in blondes); gastro-intestinal derangements, including frequent

vomiting of bile-stained, watery contents (especially on arising in the morning); aversion to fats; usually constipation or, during subacute or acute states there may be diarrhea; frequently there are psychoneuroses, especially in chronic states; a sustained decline in blood pressure to levels below 90–100 mm. systolic, and a diminished pulse pressure; presence of a positive costolumbar index, usually signifying adrenal degeneration. In addition, especially in acute or subacute states, there is an increase in the total NPN, reflecting a rise in the "undetermined fraction" of the NPN, and there may be an increase in the total calcium of the serum.[16] Other than elevation of the total NPN and urea nitrogen, there is little if any significant change in the blood, except hemoconcentration which develops during acute or subacute manifestations of the disease. An acute exacerbation, during which all of these symptoms usually are present, should always suffice to settle the diagnosis.

At a conference on the adrenal cortex, recently sponsored by the New York Academies of Sciences and Medicine, a clinical participant reported that he has observed a marked reduction in the proportion of tuberculous cases of Addison's disease during the past decade. More than half, i.e., about 60 per cent of the cases were said to have been nontuberculous. He also indicated a marked prolongation of life resulting from subcutaneous implantation of pellets of desoxycorticosterone acetate, 50 per cent of the cases surviving for seven years, although this treatment was supplemented by administration of *adrenal cortex extract* in severe conditions.

It cannot be denied that life expectancy among patients with Addison's disease has been very greatly increased since potent, nontoxic, adrenal cortex extract has become available for substitution therapy. But it can be questioned whether a toxic product like desoxycorticosterone acetate is as useful a drug as is claimed for it despite its known dangerous pharmacodynamic potentialities.

In the author's experience, as in the experience of nearly all others who have studied Addison's disease, tuberculosis is the primary etiologic factor in most cases (e.g., Addison, Greenhow, Erdheim, Kovacs). Even in those cases where an active tuberculous lesion is not found, or in cases of so-called cytotoxic atrophy of the adrenals, careful search will often reveal that tuberculosis was or could have been the principal factor in leading to degeneration of the adrenals.[2, 11, 15]

Thus a series of cases in which more than half are classed as nontuberculous in origin presents the question of reliability of certain criteria upon which the diagnosis of Addison's disease was determined. If reliance upon those criteria is not justifiable on the basis of substantial information on the physiology and pathology of the adrenal cortex, and the writer is inclined to believe that such reliance is not so justified, it could lead to error in diagnosis. Such error sometimes is suggested by the relatively large numbers of cases of Addison's disease that are reported in the recent literature.

Of course, if a significant number of cases are included that are non-Addisonian yet are classed as Addison's disease because they conform to various criteria which are relied upon, although they are not pathognomonic of the disease, it may easily mislead one into believing that tuberculosis is not the etiologic factor in most cases. Furthermore, since such cases are not as serious as Addison's disease, the possibility exists that their inclusion in a series of cases of that disease could be reponsible for unintentional misinterpretation of supposed beneficial results of therapy, including duration of survival of patients under the treatment.

TREATMENT OF ADRENAL CORTICAL INSUFFICIENCY

Clinically, adrenal cortical insufficiency generally is encountered as Addison's disease, most often resulting from tuberculous degeneration of the adrenals. Adrenal insufficiency sometimes is the result of trauma, producing hemorrhage into the adrenals, bilaterally. It is also seen in cases of adrenal hemorrhage in the newborn. Addison's disease has been induced accidentally by attempts to denervate the adrenals as a supposed therapeutic measure in surgical treatment of hypertension, diabetes, and other conditions. This results from adrenal vascular damage leading to ischemia, thrombosis, and cortical degeneration.

In the case of tuberculosis involving the adrenals, the treatment must, of course, be directed toward control of the etiologic factor, if possible. Substitution therapy, at most, can be expected to do no more than aid in recovery by relieving the hormonal deficiency, to the extent that this is possible in an organism that is handicapped by so serious a chronic disease. When the infection is under control, much more satisfactory results of substitution therapy can be expected.

Twenty years ago, the present writer developed a method of treatment for Addison's disease based on his experimental studies on adrenal insufficiency and clinical observations on Addison's disease. Prior to that time the average survival of an Addisonian was about one year; now, there are cases among which the survival period of patients, who are still under treatment, ranges up to more than 15 years. The treatment includes three essential factors: (1) Correction of the etiologic basis and its sequellae, insofar as possible; (2) facilitation of elimination of toxic metabolites; (3) substitution therapy by administration of a properly

tested, noninjurious, potent adrenal cortex extract which contains the indispensable hormone, interrenalin.[14, 15]

The etiologic factors need not be discussed here. In most cases it is concerned, essentially, with the treatment of tuberculosis. The second factor is based on the view that adrenal insufficiency represents a complex metabolic disturbance which results in the retention of toxic metabolites in the organism. It was found that this intoxication can be relieved by intravenous administration of physiologic fluids which should be employed when the blood chemical changes and clinical symptoms indicate the approach or existence of a subacute or acute exacerbation.

It may be thought that the physiologic liquids (saline solutions) act by furnishing salt to the circulation. Perhaps that is so, but the influence of the water in diluting toxic products and facilitating their elimination appears to be a more important factor. We have found that adrenalectomized dogs can be resuscitated from coma and that symptoms of adrenal insufficiency can be ameliorated by intravenous administration of isotonic liquids which do not contain salt, e.g., dextrose solution.

Since the physiologic disturbances that are the result of a deficiency of the adrenal cortical hormone constitute the principal factor in degenerative disease of the adrenals, an indispensable procedure in treatment is the administration of required amounts of interrenalin by the use of properly prepared adrenal extract, as substitution therapy. Such an extract must be capable of substituting for the loss of the adrenals in bilaterally adrenalectomized animals that do not possess accessory cortical tissue (male dogs). Test animals should be maintained alive and healthy indefinitely, or for sufficiently long periods to prove the potency of the extract and its substantial freedom from undesirable contaminants.†

Some of the proponents of the view that the adrenal cortex is the source of a number of steroid hormones, instead of an indispensable hormone, have recommended the use of certain steroid compounds, or their derivatives, for the treatment of Addison's disease and for the correction of the consequences of adrenal cortical insufficiency. In particular, one steroid compound, desoxycorticosterone acetate (DOCA) has been alleged to be an effective therapeutic agent for this purpose.

It has been amply demonstrated that desoxycorticosterane acetate not only does not act as a complete substitution therapeutic agent in adrenalectomized dogs, but that it is a highly toxic substance. Its pharmacodynamic action leads to the production of toxic hypertension, cardiac embarrassment or failure, and edema or general anasarca, especially when administered to patients with Addison's disease. Yet, clinicians have demonstrated confidence in this drug as a therapeutic agent.[17, 18] Its use should be deprecated as extremely dangerous.

A supporter of the idea that the crystallizable steroids obtainable from the adrenal represent its essential hormones[11] has stated, "In the extract of the adrenal cortex the distribution of the various active principles is such that more than 90 per cent of the physiological activity which is concerned with the maintenance of life and the distribution of electrolytes and water is produced by the amorphous fraction." He pointed out, further, that, "The administration of enormous amounts of the amorphous fraction which has been freed from corticosterone and related compounds does not produce a toxic effect and does not modify significantly the normal concentration of inorganic ions in the plasma. In contrast to this action desoxycorticosterone acetate produces a decrease in the concentration of potassium in the plasma and an increase in the concentration of the sodium and chlorine irons. Associated with these changes, the rat and dog may show prostration and extreme weakness of the muscles."

The preceding statements suffice to indicate the mistaken premise, if there is any basis, for the use of DOCA as a therapeutic agent in adrenal cortical insufficiency. Since it is admitted that more than 90 per cent of the activity of the adrenal is represented by the amorphous (steroid-free) fraction of an active adrenal extract and that this can substitute for loss of function of the adrenals by supporting life and good health in adrenalectomized animals, why should anyone think of administering a dangerous toxic steroid when a harmless yet active hormone-containing extract of adrenal cortex is available?

We have not found it necessary or useful to limit the diet of Addisonians to foods which contain but little if any potassium, as has been recommended by some clinicians. The amount and kind of food that patients with Addison's disease ordinarily eat does not contain enough potassium to be injurious. Furthermore, at the time when an increase of potassium in the blood might be significant, if present, i.e., during a crisis, total anorexia exists and food of any kind, if taken, is vomited. Usually, a reduced protein and an increased carbohydrate diet has been found to be most favorable for Addisonian patients.[14, 15]

Another practice which has been generally employed is the administration of salt in the form of tablets. This is not only unnecessary but is undesirable. All patients who can retain food can obtain an

† Extracts that are available through license under the basic Rogoff and Stewart U. S. Patent No. 2,096,342 are required to be capable of fulfilling the conditions of this test.

ample excess of salt in their diet by using more than usual as seasoning. As indicated in the foregoing, the principal value of salt would be to increase thirst and thus augment the intake of water to "flush out" toxic metabolites. An important objection to the administration of large amounts of salt by stomach, in any form, is the fact that the gastro-intestinal tract is already irritable in Addison's disease and the presence of excessive amounts of salt in the stomach may cause greater irritability and vomiting.

SUMMARY AND CONCLUSIONS

The author believes that the idea that the adrenals secrete a number of steroid hormones instead of the secretion of an indispensable hormone is untenable. It is not adequately supported by unquestionable physiologic evidence. It is based chiefly upon observations related to pharmacologic or toxic effects of compounds derived by extraction of adrenal tissue, or prepared synthetically, not upon quantitative or substantial qualitative physiologic information.

As a result of that idea, desoxycorticosterone acetate (DOCA) has come into use as a therapeutic agent and has been responsible for dangerous reactions, even death. It cannot be said to represent the adrenal cortical hormone and is not a useful substitute for loss of the indispensable adrenal function.

More substantial evidence supports the original view that the adrenal cortex elaborates and secretes a hormone which is essential for life and good health. Loss of function of that hormone results in a complex metabolic disturbance which produces the clinical and physiologic characteristics of adrenal insufficiency. The effects of adrenal insufficiency can be best combatted by the administration of the hormone (interrenalin) contained in a suitably tested, potent extract of the adrenal cortex.

Diagnosis of adrenal cortical insufficiency by blood-chemical tests for sodium and potassium is unreliable and misleading. There is no one factor among the phenomena that are observed in adrenal insufficiency that can be considered pathognomonic. Attempts to correct any one or more single manifestations of the complex disturbance are not physiologic. Some of the alleged successes among such therapeutic reports can possibly be explained on the basis of probable errors in diagnosis of adrenal cortical insufficiency, or Addison's disease. This possibility is suggested by the seemingly large number of cases of that disease which have been reported in recent literature.

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This paper presents the viewpoint that there is a psychosomatic basis for at least some of the cases of obesity.

The Pathogenesis of Obesity.

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The purpose of this paper is to re-emphasize a concept of obesity as a psychologically induced functional disorder of the "appetite-regulating" center in the hypothalamus.

THE RELATION OF THE HYPOTHALAMUS TO OBESITY

There recently has been an increased interest in the mechanism of obesity induced in experimental animals by injury to the hypothalamus.[1] Briefly, the facts can be stated as follows: When bilateral hypothalamic lesions are produced in the rat, dog or monkey by means of the Horsley-Clarke steriotatic apparatus, the great majority of animals soon begin to eat two to three times the amount of food eaten by their littermate controls and hence soon become quite obese. These animals were somewhat less active than controls not operated upon but the increase in weight is out of proportion to the reduced activity.

Neither the pituitary gland nor the nervous pathways between the pituitary and the hypothalamus play a part in this hyperphagia.

Long [2] and his associates found that the obesity is produced only if excess amounts of food are presented to the animals, and starvation results in the expected loss of weight. However, limitation of food must be severe and permanent to prevent obesity from developing.[3] The basal and total oxygen consumption in injured and control groups show no abnormalities and it has been concluded that the obesity is apparently a result of increased appetite and is not a metabolic disorder.

It is interesting and perhaps important to note that a destructive lesion a few millimeters below the hypothalamus, i.e., the pituitary gland, produces severe anorexia with subsequent cachexia (Simmond's disease).

At any rate, one can definitely state that the experimental production of a specific hypothalamic lesion leads to an increased "appetite," and to the failure of the as yet unknown mechanism which regulates energy exchange.

Teleologically, one can postulate that like the vasomotor center, the respiratory center, the body temperature regulating center, the sleep regulating center, there is an "appetite regulating center" in the diencephalon. This center so regulates the nervous system that a psychologic and somatic feeling of satiety is reached when the energy value of the food eaten reaches an equilibrium maintaining energy balance. That center tells us when we have had enough! It would explain how one can live for years without a conscious thought of calories or carbohydrates and yet maintain the same weight in spite of great irregularities in diet and activity.

If one may make another assumption, let us say that we may have a similar hyperphagia without a necessarily destructive organic lesion. That is, there may be a functional alteration without demonstrable anatomic damage. Wilder [4] was probably the first to suggest the presence of an "appetite regulating" center in the midbrain, and that malfunction of this center would raise the satiety threshold. Bruch,[5] too, believes that the sensation of satiety does not function adequately in the obese. The resulting excessive intake of food results in obesity.

THE HYPOTHALAMUS AND EMOTION

If the hypothalamus is involved in human obesity via dysfunction of an appetite regulating center, in what way may psychologic factors play a role?

The hypothalamus is the chief co-ordinating or integrating center for autonomic functions. In it are "neural patterns responsible for emotional expression and behavior which are normally inhibited by the cortex, and it is in the cortex that feelings of emotions are evoked. Both activities exist in the normal person in co-operation." [6] Stimulation of various areas of the hypothalamus can produce almost every effect mediated by peripheral sympathetic fibers. The sympathetic discharges in cases of strong emotional excitement are dependent on central mechanisms localized to the hypothalamus. Similar evidence lies in the "sham rage" of decorticate cats, exactly reproduced by pure hypothalamic stimulation.

Furthermore by stimulating the normal human hypothalamus by means of a directly placed electrode, Grinker [6] was able to produce the objective and subjective emotion of *fear*. He also was able to show the similarity of electric, pharmacologic, biologic and *emotionally laden verbal stimuli* in hypothalamic and cortical excitation. In fact, emotional stimuli given once caused prolonged discharges which gradually became feebler. There was, in short, evidence that emotions influence intellectual processes through "the mechanism of the hypothalamus driving the cortex." And Grinker concludes,

> As a cephalic representative of the autonomic nervous system, the hypothalamus has to do with energies of visceral origin which are the forces of the instincts. It controls activities of the periphery in metabolism, balancing the constructive and destructive tendencies, and it forces activities of the cerebral cortex. It represents tensions or "cravings" within the autonomic nervous system (instinctual) which are precipitated and co-ordinated in the hypothalamus rather than expressed individually and inco-ordinately. Its transmitted tension stimulates activity within the somatic nervous system, including the cerebral cortex, into a search for adequate stimuli (food or sex), which stimuli release tensions and end in visceral quiescence.[6]

Foster Kennedy [7] says, "It (the hypothalamus) plays a part in conditioning moods of elation and depression, and their expression in laughter and weeping. It is concerned with reactions of defense, aggression, suspicion, fear, anger, sex."

The hypothalamus has also been described as an autonomic center concerned with maintaining a constant internal environment. (Satiety.)

It may be concluded that the hypothalamus is a vital center concerned in the complex interrelations of the autonomic and cortical nervous systems essential to the expression of emotion.

EMOTIONS AND EATING

Many writers, artists and scientists have long recognized the close association of emotions and eating. Recently a renewed interest in this problem has appeared. Similar statements run through these reports. Thus MacBryde [8] writes that when "satisfaction of other types are denied, the pleasures of eating may serve in their stead." And Alexander [9] writes, "The most constant and significant fact seems to be that in all cases the disturbance of eating is a reaction to emotional frustration."

It would seem that two factors play a dominant role in the psychologic background of these patients; namely, lack of affection and closely allied to it, frustration. Lack of affection as used here implies a need for love, in the wide sense of the word, for security, care, respect, for some degree of importance in one's own eyes. Similar conclusions were made by Bruch,[5, 10] Alexander,[9] and others.[11]

While it is true that all of us have been in situations leading to frustration and/or involving lack of affection, it seems that in many obese people these situations are particularly painful, and these people seem to be excessively sensitive in this regard.

An interesting and clear story was obtained from a 21-year-old girl (weight 185 pounds) who remembered that when she was a child her father, a wholesale candy merchant, would give her candy to "quiet" her if she would cry or be especially upset. Even now, she says, when she is under stress, she becomes hungry. She gets relief by eating. (Was a conditioned reflex established?)

Here it should be mentioned that Brooks [12] recently has found that when a rat with induced hypothalamic injury was "angered by handling and then returned to its cage, it immediately attacked its food cup and usually began to eat." Furthermore, immediately postoperatively and later, any trifling disturbance caused these rats to "bite, struggle, and eat."

The first pleasurable sensation we know as infants is that of feeding, associated with this is a sense of affection and security. How often we find mothers who give their child the bottle to keep them quiet, and how easily it is found that food satisfies the baby.

In her study of obese children,[10] Bruch found that to all mothers of such children food stood for more than its caloric value. It represented health and security and, more often, love and affection. The majority of the children, incidentally, were exposed to over-protection and exhibited signs of immature behavior in other respects.

Richardson [13] writes, "The strength of the craving for food and the equation, food equals affection, suggests a deprivation early in the life of the obese individuals." The demand for pleasure and/or affection in later life is satisfied by the ingestion of excessive calories through an association made early in life. In other words, there is a reversion to an infantile *food-satisfaction* stage—the oral-fixation stage of the psychiatrists. Alexander [9] believes that an increased craving for love and aggressive tendencies to grab or to possess form the unconscious basis of the excessive appetite.

One can postulate that under certain situations of stress, specific to the psychology of the individual patient, a storm of autonomic nervous system impulses is released. These impulses impinge on the hypothalamus, disturbing therein the function of the "appetite regulating" center. The fine adjustment regu-

lating caloric intake is knocked out of gear and the patient finds relief of his tension, or a substitute satisfaction, by excessive eating. Such a state prolonged could conceivably lead to chronic prolonged hyperphagia and subsequent obesity.

Of course, obesity itself may lead to a certain amount of internal unhappiness because of ridicule or social ostracism, with again frustration and lack of affection.

It is of interest to note how tenaciously the obese cling to their abnormal weight in spite of insults, ridicule, propaganda and medical health statistics. Why do they remain fat? Because their very obesity makes them receive less than their required affection, and so their obesity leads often to a frustration of ambition and desires, secret or overt. The vicious cycle is perpetuated.

A sentence from Richardson's paper [13] is apt, "she eats as if to fill a boundless void." This void is the emptiness perhaps of their inner lives, which by a cruel fate becomes the void of an empty stomach.

No one can deny that in many cases, if not all, heredity eating habits and muscular activity play a role in the obesity of any one patient. But that these factors do not play the dominant role is seen from even a brief study of the many people who remain thin, or at least not fat, although obesity may "run in the family," or a study of those patients who lead very sedentary lives.

One may suggest that since postmenopausal obesity is not consistently found that perhaps, here too, the psychic trauma consequent to this upheaval in emotional, sexual and social spheres lead some (those predisposed?) to turn to food unconsciously as a compensation for a lack of the affection they need. Furthermore a number of women gain weight soon after pregnancy and it is possible that similar mechanisms are involved.

TREATMENT

Too often the diagnosis of hypothyroidism is applied to the obese. On the contrary, Plummer [12] found that most patients with true myxedema do not become obese. Their appetite regulating center functions normally and adjusts for the reduced metabolic rate. In another series only one of 25 patients with myxedema was obese.

The futility of giving thyroid extract to the overweight patient with a normal thyroid gland is emphasized by the work of Winkler [15] and associates. They showed that the patient with a normal thyroid gland can inactivate moderate doses (3 to 4 gr. a day) of desiccated thyroid. If large doses are given, the increased appetite of the induced hyperthyroidism neutralizes the effect of the stepped-up metabolism.

In a long-term study of obesity, Danowski and Winkler [16] found that while the immediate effect of a low caloric diet was a reduction in weight, a permanent weight loss of 30 pounds or more was obtained in only a few patients. They concluded that changing the *eating habits* of the obese is the essential part of successful therapy.

This is another way of saying that the regulation of appetite must be altered to a different level. The problem is not simply one of bad habits, but of changing the person's reaction to an emotion-charged situation by overeating. The patient must understand the mechanism of his reaction.

More and more attention is being directed to the psychosomatic features of obesity. Nicholson [17] reported that psychotherapy alone was successful in 26 of 38 obese patients, success being a follow-up of at least one year and a weight loss of 5 kilograms or more. (These are rather lenient criteria.) Only 9 of 35 on an 800 calorie diet were successful in maintaining weight reduction. In this series amphetamine and thyroid alone were completely unsuccessful.

This is not meant to minimize the essentiality of a reduced caloric intake, but merely to emphasize that unless the psychologic factors are discovered and discussed, the patient will probably eventually return to his old weight. Reduced caloric intake plus psychotherapy is required. It is not enough to say that people are fat because they eat too much; it is necessary to find out *why* they eat so much.

SUMMARY

There is no doubt that the usual case of obesity is a result of the ingestion of excessive food.[18] But why the patient eats more than he needs is not so clear.

As many others have suggested, the *susceptible* person, often because of frustration and lack of affection, gets his relief or satisfaction by excessive eating, the psychologic mechanism being the ingrained infantile association of food and affection.

It is also suggested that the somatic aspect of this problem is that the *appetite regulating center* in the hypothalamus (the evidence for which is only experimental) is set at an abnormal level by way of the autonomic nervous system with which it is connected. That is, there is a psychologically induced functional disorder of this appetite regulating center in the hypothalamus, with the production of hyperphagia and obesity.

Therapy must include psychologic diagnosis and guidance to be permanently successful.

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WHAT'S YOUR DIAGNOSIS?

A 43-year-old colored woman was admitted to the Medical Service for the fourth time on September 6, 1940 and died October 7, 1940. She was first seen in this hospital in July 1928 with pain and swelling of the ankles and knees, cough and pain in the left chest. X-rays showed enlargement of the hilar lymph nodes. Numerous sputum examinations were negative for acid-fast bacilli then and subsequently. A secondary anemia was present. One year later she complained of poor vision in the left eye but no abnormalities were found. In 1930 she was seen because of right lower chest pain and shortness of breath. The heart was slightly enlarged to the left; the rhythm was irregular and a loud apical systolic murmur was described. Blood pressure 150/90. EKG revealed frequent premature ventricular contractions. Retromanubrial dullness was thought to be increased. Fine râles were heard at the lung bases. An ophthalmologist suspected beginning left optic atrophy. Blood and spinal fluid Wassermann tests were negative and remained so on subsequent tests. In 1934 she developed iridocyclitis with secondary glaucoma in the right eye. A partial superior irridectomy was performed and she recovered her sight in the right eye. She was seen frequently in the outpatient department because of shortness of breath, chronic cough, with moderate amounts of sputum. Bronchograms with lipiodol revealed mild bronchiectasis. A bronchoscopy in 1937 was essentially normal. X-rays of the chest showed rather marked fibrosis, particularly in the bases. Widening of the aortic shadow in the region of the innominate artery was noted and considered suggestive of aneurysm in 1936. The condition of her heart and lungs remained essentially the same, although there was some variation in the amount of the cough, sputum and dyspnea. Apparently there was never any ankle edema, but râles were almost always heard at the bases.

She developed generalized lymph node enlargement with matted firm, nontender nodes in the femoral and right supraclavicular regions. Splenomegaly was noted in 1939. A fibromyoma of the uterus was also found.

In March 1940 she was again admitted with fever

LABORATORY DATA

Blood.	Sept. 6'40	11	14	16	20.	22	24	25	28	Oct. 2	5
RBC	3,920,000									3,900,000	
WBC	6,050		11,250		10,100			7,200	4,950	5,300	
Hgb. (Gm.)	11					11.6	12			10	
Differential											
Stabs	4										
Seg.	76				77						
Lymph.	18				21						
Mono.	2				1						
Smudge					1						
NPN (mg. %)	38	40		44							38

Kahn, negative; Wassermann, negative.
Total Serum Protein (10/5) 5.82 Gm. per cent; albumin, 2.47, globulin 3.35.

Urine. (Five specimens) Specific gravity 1.005 to 1.024; 1+ albumin in two specimens; sugar negative. Few WBC and rare RBC except in last specimen on October 3 which contained 100 WBC/hpf. Fishberg test, 1.032 concentration.

Stool. Negative.

Sputum. Five sputum cultures and smears revealed predominantly Staphylococcus aureus. All smears were negative for acid-fast bacilli. Guinea-pig inoculation was negative.

Electrocardiogram revealed a sinus tachycardia, premature ventricular contractions, low voltage and inverted T_2 and T_3. These changes were interpreted as indicating myocardial disease and digitalis effect.

Chest X-Ray. (9/7/40) Diffuse infiltration in region of hilus fading slightly toward periphery.
(9/18/40) Right lung shows an increase in infiltration throughout.

and anemia in addition to the previous findings. She remained in the hospital from March 29, 1940 to June 14, 1940. During this time she had a daily fever up to 103°. She was treated with transfusions, neoarsphenamine, and 1,600 R units over each of two portals to the back and front of the thorax. There was a persistent leukopenia throughout her hospitalization and following the radiation the white count dropped to as low as 1,780 cells. Total serum protein 8.10, albumin 3.36, globulin 4.74 Gm. per cent.

The final admission was on September 6, 1940. For the previous three weeks there had been increasing dyspnea, orthopnea, severe paroxysms of coughing productive of frothy, whitish sputum. She had a shaking chill two weeks before admission and had fever from then until she was admitted. Pain in the right axilla that was not related to respiration developed one week prior to entry.

Examination. T. 99.4°, P. 100, R. 24, B.P. 130/80. She was an emaciated colored woman of about 40. She was very dyspneic and orthopneic and coughed occasionally. There was slight pitting edema of the thighs but none of the ankles. Skin was not remarkable. The left pupil was larger than the right. Right pupil was deformed by an old well healed partial iridectomy. Both pupils reacted well to light. There were numerous pigmented areas in the retinae. Ears, nose, mouth and throat were not remarkable except for carious teeth and pallor of the mucous membranes. The trachea was deviated to the right. The lymph nodes were generally enlarged to a moderate degree. There was an inspiratory lag and diminished expansion of the right upper chest. Medium moist râles were heard over most of both lung fields. The heart was slightly enlarged to the right and left by percussion. The rhythm was irregular. There was a long, loud, harsh systolic murmur heard along the left sternal border and loudest in the fifth interspace about 5 cm. to the left of the midline. No diastolic murmurs were heard. The spleen was greatly enlarged, reaching almost to the umbilicus. The liver was down 1 to 2 fingersbreadth. No other organs or masses were felt. There were no abnormal neurologic findings.

Course. During the first week in the hospital she seemed to improve. Temperature ranged around 99° during this time. On the ninth hospital day her temperature suddenly rose to above 105°, and the pulse to 148/min. She developed marked respiratory distress. Signs of consolidation developed over the right chest. She improved after receiving sulfapyridine and being placed in an oxygen tent. A pleural effusion developed on the right. The fluid was sterile. Smears and guinea-pig inoculation were negative for tubercle bacilli. About one week later a similar episode occurred and her subsequent course was characterized by recurrent episodes of cough, dyspnea, chest pain and vomiting. She died on October 7, 1940, during a paroxysm of coughing.

For answer, please turn to page 56

Technics of Value in Examining Small Children

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Examining small children is such an unpleasant task to many general practitioners that an outline of some technics that have proved of value in my own limited experience, as a "family doctor" in a small town, seems justifiable. Most of the ideas presented here are not original but have been gotten from textbooks of pediatrics, journals and word-of-mouth statements by physicians who have had years of successful experience in examining and treating children.

Before discussing the setting, approach, and actual procedure of examination, a clear statement of the chief principles involved is of paramount importance. The first essential is to gain the child's confidence and to determine quickly his mental attitude.[1] The degree of co-operation given by the child depends on the physician's ability to gain this confidence, allay his fears and to create a friendly, pleasant atmosphere.[2] Considerable tact and frequently an enormous amount of patience are required.

SETTING

The ideal setting for the examination of small children is an office that appears to be and is arranged as nearly like an average American home as is practicable.[3] The reception room can fulfill this requirement in almost any office and the actual room used for examining children should be free of furnishings and equipment that will frighten an already apprehensive child. When a small children's waiting room, with appropriate pictures, furniture and toys, can be provided a good beginning toward inspiring confidence and minimizing anxiety has been made. Lacking this, some points that improve the average reception room's acceptability to children are baby pictures on the walls (some practitioners like to cover their walls with pictures of babies they have delivered), children's chairs and an assortment of toys, books or puzzles.

Clothing worn by the doctor and his office personnel should be of a type that will not alarm the child. Starched uniforms, flashing head mirrors or long white coats are often frightening to small children. The nature of the doctor's practice will dictate the degree to which he can meet this requirement. The nurse or receptionist who slowly, smilingly approaches the young caller and kneels or stoops as she addresses him so that he won't have to strain to look up at her, will get the interview off to a much better start than the abrupt, stern approach of the uniformed nurse or doctor with outstretched rectal thermometer. It goes without saying that a natural liking for children on the part of the doctor and his helpers will be a great asset in making the examination successful.

APPROACH

The successful approach depends in large part on the physician's ability to place himself at the mental level of his patient. Particularly to the apprehensive child, the physician should appear quiet, friendly, unhurried, unruffled and pleasant. An effort should be made to amuse the child by some simple act appropriate to his mental level. Making clicking or whistling sounds may be appropriate to interest an infant, but "woe be unto him" who insults the intelligence of the school child with some pre-school triviality. Riddles or toys may be helpful.

At all times the physician must appear natural and be truthful, for the child is quicker to detect sham than many realize. Once confidence is lost in some discovered deception, difficulties multiply. The physician who remains calm, is firm but gentle with the unruly child, is more likely to succeed than one who shows his irritation.

Generally, and especially when dealing with a shy child, it is best to begin the interview by talking with the parent who brought the child. Information thus

gained as to the chief complaint and the parent's story of the illness will help in forming the plan of approach to the patient himself. During these minutes the child will have a chance to size-up his surroundings, to learn that nothing catastrophic will happen to him (at least with the suddenness that he might have feared from experience in some previous abrupt and ill-planned examination). During this period a small child may be more at ease if he is allowed to browse around a few minutes. (Right here should go a tip that "breakables" and dangerous equipment should be placed out of the toddler's reach.) There are occasions when the over-solicitous parent should be tactfully excluded from the room so that the child may be interviewed alone or with the aid of a nurse.

After the history is completed, allowing the alert youngster ample opportunity to amend his parent's story or tell his own, the preparation for the actual physical examination should begin. Letting the child handle the stethescope, trying it out on a doll, or listening to his heart-beat may make for an easier beginning. At times the mother can slip the bell against the child's chest, move it about as the physician signals and most of the examination of the heart and lungs can be conducted without the child becoming aware that the examination has begun. Once I had the experience of completing the history and examination and having the five-year-old walk out saying, "Mama, when am I going to see the doctor?"

EXAMINATION

Examining a child under two years of age or a very sick child necessarily calls for some modification of the plan outlined below for the average small child. One must let the sick baby remain in the most comfortable position possible, checking the heart and lungs as the mother holds him against her shoulder. It is of special importance to use a minimum of restraint and to omit all procedures not absolutely essential to the acute case at hand.

During the interview one will have had ample opportunity to observe many things about the patient, his alertness, mental and emotional attitude, evidence of pain, skin, posture, mannerisms, speech and coordination. By getting a full history and noting all that is possible to note before starting to undress the child to place him on the examining table, one can make the actual physical examination brief, rapid, systematic and skillful. One garment should be taken off at a time as the examination proceeds. The orthodox method of recording the examination by systems is usually followed but it is more often advisable to listen first to the heart and lungs while the patient is quiet, then go on to the abdomen, extremities, nervous system, and finally the head. One can almost always depend on having an open mouth through which to view the throat with minimal help from a tongue blade if he completes his check-up below the neck then thoroughly examines the ears with an otoscope. Having the mother hold the infant's arms up alongside his head as he is lying down aids in visualizing the throat.

When called to the sick child's home, the physician should enter the sick room as any other friendly visitor, exposing his identifying examining equipment only after the young patient has gotten used to his presence. Usually the examination will be more limited here than it would be at the office, though nothing should be sacrificed that is required to make an accurate diagnosis and start adequate treatment.

CONCLUSION

In conclusion, ten handy tips for the family doctor as he cares for children should be listed.

1. Provide the child something to play with while he waits to see you.

2. Keep knives, needles and other unpleasant equipment out of sight.

3. Place a trimmed, inverted bottle nipple on the end of your stethoscope bell to prevent startling babies with cold metal or plastic.

4. Warn the child in a gentle way that the needle will hurt a little. (Like a mosquito or henpeck, like this, with a little pinch.)

5. Have nurse or assistant do the sticking—preferably in another room.

6. Reward the child for good behavior—empty vials with rubber caps as doll nursing bottles for girls; tongue blades crossed and bound by a rubber band to form airplanes for boys.

7. Very apprehensive children can be given essential injections while they sleep at home—a little novocain in the syringe helps.

8. Warn parents against threatening their children that they will "send for the doctor" as punishment, and thus avoid a bad "build-up."

9. Make medicines palatable: liquids for little tots; apple butter or jelly will help "down" a pill; lozenges are "candy."

10. Have Father bring Junior next time if Mother proves unable to handle the situation.

Finally, the physician should like children and be

able to see things from their point of view. The physician who doesn't like "the brats" and detests treating them, should refer them to a colleague who does and at one stroke rid himself of a nuisance and gain the gratitude of the child, his parents and his medical colleague.

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Prophylaxis of Hemolytic Disease of the Newborn

Routine testing of the sera of all Rh-negative mothers during their pregnancies makes it possible to predict rather accurately the possibility of the occurrence of hemolytic disease in the child when born. This has enabled the physician to have available Rh-negative blood of the proper group for transfusing the baby and has reduced the mortality rate for these babies considerably. Such treatment, though helpful, is far from ideal since it is inapplicable to those cases where the infant is stillborn or aborted before term.

In a paper recently published (*American Journal of Obstetrics and Gynecology*, July 1947) Kariher reports three cases in which prophylactic treatment of the pregnant mothers was attempted and appeared to have a large measure of success. The idea was to try to prevent by chemical means the completion of the antigen-antibody reaction which is fundamental in the production of hemolytic disease. The treatment consisted of weekly intramuscular injections of 2.0 cc. of a solution of ethylene disulfonate during the last three, four, and six months of pregnancy, respectively.

In all three cases the patients had previously delivered one or more infants which had died of hemolytic disease of the newborn. This was well substantiated by blocking and agglutination tests to show that the mothers were sensitized and autopsy reports on the infants in which the pathologists made the diagnoses of erythroblastosis fetalis.

In two of the cases the hemolytic disease of the previous pregnancies were due to Rh-incompatibility. In the other case it had been due to O-A incompatibility, the mother being group O and the infant group A. Each mother already carried a high titre of antibodies in her serum when the treatment was begun. While the treatment was in progress the titre of the antibodies in the maternal serum was carefully tested at weekly intervals. In each case the titre of the various antibodies fell from relatively high to relatively low levels during the period of treatment. The pregnancies went to term and in two cases entirely normal Rh positive (1 case) and A_2 (1 case) babies were born. In the third case the Rh-positive infant showed evidence of hemolytic disease on the third day after birth, but this was controlled by several blood transfusions of about 70 cc. each. After discharge from the hospital on the 19th day its course was uneventful.

According to the present state of knowledge all three of these babies would have been expected to exhibit severe cases of hemolytic disease of the newborn if the mothers had been untreated. One of the most remarkable aspects of the experiment is that the solution of ethylene disulfonate used contained such a minute concentration of the drug ($1:10^{-15}$) that the author is reluctant to attribute the good results to it, but rather postulates that they may have been due to the injection of practically pure distilled water. Dr. Kariher does not claim that this is a cure for hemolytic disease of the newborn, but hopes that others will attempt to corroborate his findings.

One of the characteristics of modern medicine is the growth of auxiliary services placed at the disposal of the physician. Among these, that of social service ranks high when employed properly. This article should be read in conjunction with the editorial appearing in this issue.

The Role of the Social Worker in Medicine

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The medical and psychiatric social case worker may play an important role in the practice of good medicine, where it is desired to obtain the maximum of therapy and homeostatic adjustment for the patient.

Recently physicians, in general, have become more appreciative of the role which the social worker plays in the over-all therapeutic picture. It is thought that the realization of the importance of social workers has been somewhat obscured in the past because of the unfortunate association of social work, and those who engage in social work, with the members of the "idle 400" who did "charity work" for the underprivileged. Fortunately this misconception has been gradually replaced by the knowledge that present-day social workers are experienced, effective, well-trained specialists. Accredited social workers must have, in addition to a bachelor's degree, some graduate training in the social service field, both in supervised case work and in didactic studies. Field work corresponds to the physician's internship, and provides for an introduction into the interpersonal field which social work requires. It is not the purpose of this paper to review the varied requirements necessary for adequate training of social workers. Rather it is to clarify several pertinent issues in regard to the relationship among the physician, the patient and the social worker.

Social workers aid the physician both in the medical (surgical) and psychiatric fields, and in each, attempt to create a working liaison between the physician and the patient, and the patient's family. This may be accomplished by social workers in the social service department of a hospital or clinic, or by workers in family and children's agencies, when clients of these agencies need medical care. The medical and psychiatric case workers attempt to help the patient and the patient's family to adjust to the patient's illness, and its concomitant difficulties.

Because the widespread concept of psychosomatic medicine—that one must treat the patient and not the patient's disease alone—has been accentuated, there has been an increasing emphasis placed on the patient's personality structure and the patient's problems. The physician no longer deals with disease entities but with a patient afflicted with disease. The patient is an individual who requires adjustment to his illness, to the change in environment concomitant with illness, to the economic problems associated with protracted illness, and in chronic disease, to a new life pattern. The patient's fears in regard to his illness, and in regard to his numerous social problems which evolve as a result of his illness, must be allayed. A patient is never completely divorced from his environment, never totally released from the tensions caused by economic and social pressures created and perpetuated by the culture in which the patient lives. These pressures and tensions in themselves may be the inciting factors of a disease process, or they may produce exacerbations of an already existent pathology by increasing the functional component of the disturbed physiology, with an intensification of complaints. Most patients are aware of their illnesses, and exhibit some type of concern over them, either verbally or by other behavior.

It is necessary to alleviate early the patient's fears, fears which often are based upon ignorance or misinformation gleaned from well-meaning relatives or friends, for such fears may be the beginning of a neurosis. Illness as it is regarded by the patient is often catastrophic, regardless of the mildness or severity of the underlying physical process. An understanding of the patient's philosophy is necessary for the rational management of the case.

It is here that the medical and psychiatric social worker is most valuable. Necessary emotional support, intelligent aid in an effort to help the patient adjust to his intolerable situation, extension of pertinent histories, and active liaison between the overtaxed physician and the patient's relatives, are readily achieved by the trained social worker. The need for such co-operation is especially evident in large institu-

tions in which the lower economic group receives care. For these people, particularly, even temporary illness may mean depletion of their life's savings.

The prevention of a neurosis is a battle well won, for it is important to remember that the neurotic who is incapacitated by functional symptoms is as ill as a patient with pneumonia and is as much a loss to the community as to himself. The social worker in the charity hospitals, as well as in the private pavillion, can do much to alleviate the feeling of aloneness and wonder about the physician or intern assigned to any particular case, by giving support to the patient and decreasing his fears. It is important to remember that the physician, as such, is feared because of the colored emotion which has been focused upon medicine and illness in general. The seeking of aid from a doctor, in some cases, signifies the patient's admission of failure; that he has finally decided, with reservations, that he is ill and that further attempts at self-medication are futile. As time passes the patient feels relieved that the responsibility for his care is out of his hands and is entirely the responsibility of the physician. At this stage both the physician and the social worker have the greatest opportunity to help the patient, for both can give reassurance that there is a disease state present which may be alleviated through adequate treatment, that there has been a transitory illness which has declined, or that further observation is necessary before a definite diagnosis can be given. It is important not to be in error at this stage, as improperly chosen words may initiate marked anxiety and fears, and culminate in a neurosis.

The patient-physician relationship and the establishment of rapport is most important for successful treatment, and the successful development of this situation can be hastened and strengthened by a few well-chosen words from the social worker during the patient's interview.

The work of the medical or psychiatric social worker should not be considered subordinate to the physician's, but should be thought of as a concomitant therapeutic agent. Each mutually supports the other and works towards a common goal. The work of the psychiatric case worker is not limited only to adjunctive aid, but in many instances consists of actual treatment sessions, both with the patient or patient's relatives, in an effort to aid the patient to see his own difficulties at home and in his social pattern. The patient is seldom directly told how to handle his difficulties by the worker but is helped to gain insight into his problem by well directed methods. In those cases where the patient is unable to gain insight, and is incapable of manipulating his environment, the social worker may enlist the aid of various community resources.

The attitudes of some physicians, their intolerance and lack of patience with regard to social workers and their ability, have caused some social workers and agencies to feel that the doctors are antagonistic and unco-operative. By this attitude and the resultant loss of the case worker's co-operation, the physician has unwittingly caused the patient more harm than his medical knowledge can undo. In some cases where the patient is under psychiatric management by an unfeeling, unoriented psychiatrist, the psychiatric social worker, studying the patient from a broader scope, is more capable of instituting a satisfactory relationship with the patient. It is unfortunate that only too often the worker is justified in her appraisal of the physician's antagonisms.

The use of the medical and psychiatric case worker should be considered on a differential basis. When the social worker can be of assistance, good medicine requires that she play her role in the treatment process. The medical and psychiatric social worker should be considered as essential to efficient clinical practice as are the x-ray technician and laboratory worker.

Summary. The need for medical and psychiatric social case workers in the field of medicine is defined and stressed. Some of the misunderstandings, detrimental to the patient-physician-social worker relationship are aired and suggestions for bettering the therapeutic mechanisms for the patient are made.

2501 West Devon Avenue.

Answer to Quiz Case (page 50)

Diagnosis: Sarcoidosis.

Diagnosis was established before death by biopsy of a cervical lymph node; confirmed at necropsy.

CASE REPORT . . .

Complicated Dextrocardia with Partial Heterotaxia*

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It is generally recognized that when the heart alone is transposed (isolated dextrocardia) other congenital cardiac anomalies are nearly always present. Lichtman [1] in his series of 161 cases, collected from the literature, found only three cases uncomplicated by other developmental cardiac anomalies. On the other hand, dextrocardia accompanied by general transposition of the viscera (heterotaxia) is rarely complicated by striking developmental malformation of the heart.[2] The following case of dextrocardia is therefore of interest, for a grossly malformed, dextroposed heart was associated with partial transposition of the abdominal viscera

CASE REPORT

A five-year-old white male with congenital cyanosis was admitted to this hospital because of frontal headache and fever of two weeks' duration. Dyspnea had limited activity to minimal exercise and play. There had been no edema of the extremities or ascites. At nine months of age a right hemiplegia had been recognized. This persisted for six months.

After admission, temperature, pulse, respirations, and white count rose progressively and two weeks later signs of cerebrospinal meningitis, including rigidity of the neck and frequent bedwetting, were evident. There was clubbing of the fingers and toes. On percussion the cardiac dullness lay to the right of the sternum and the cardiac impulse was palpable in the right fifth interspace in the midclavicular line. A harsh blowing systolic murmur was heard over the entire precordium. The blood pressure was 105/85 in both arms. There was no residual evidence of the old right hemiplegia.

Laboratory Investigations. The hemoglobin was 120 per cent (Sahli) with 8.5 million erythrocytes per cu. mm. The white count was 22,000 per cu. mm. with 67 per cent polymorphonuclear leukocytes.

Roentgenograms (Fig. 1) showed the right-sided position of the heart with elevation of the left leaf of the diaphragm and a tortuous left pulmonary artery. Barium studies revealed the stomach and jejunum to be in the usual position, but the ascending colon, cecum, and appendix were transposed to the left lower quadrant.



FIG. 1. Roentgenogram of trunk to include chest and abdomen. Note dextrocardia, large left lobe of liver, and elevated left diaphragm. From X-ray Department, Babies' and Children's Hospital, The University Hospitals, Cleveland, Ohio Dr. York.

* From the Institute of Pathology, Western Reserve University and University Hospitals of Cleveland, O.

Electrocardiograms (Fig. 2) showed abnormal left-axis deviation with inversion of T waves in leads 1 and 2. The P wave was upright in lead 1 showing that the direction of auricular excitation was normal which is unlike the electrocardiogram of situs inversus in which all of the waves of lead 1 are inverted. A.V.L. (unipolar potential of the left arm) indicated that the main mass of muscle faced the left arm. Ruskin [3] and associates, in reporting a case of isolated dextrocardia, published an electrocardiogram which showed an upright P and a tall R in lead 1 as in the electrocardiogram of this case.

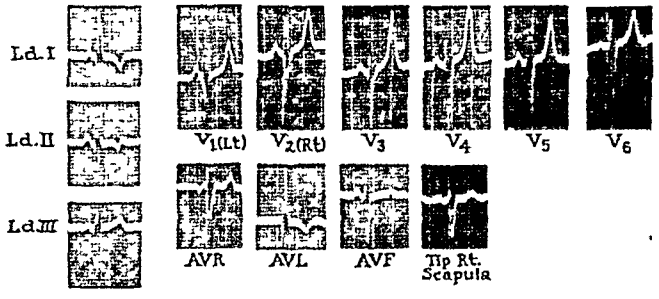


FIG. 2. Leads 1, 2, 3 and AVL show evidence of abnormal left-axis deviation. The P and R waves in lead 1 are evidence that cardiac excitation is in the normal direction.

Hospital Course. Repeated lumbar punctures revealed a cloudy spinal fluid with high proteins and a large number of leukocytes. On the 32nd hospital day a culture of spinal fluid revealed pleuropneumonia-like organisms. Chemotherapy and other supportive treatment failed and the patient died on the 43rd hospital day. The clinical diagnoses were: acute cerebrospinal meningitis due to pleuropneumonia-like organisms, tetrology of Fallot and possible cerebral thrombosis. A report of the bacteriological aspects is to be given in a separate paper by Dr. H. J. Carlson.

Autopsy (No. 9351) revealed acute, suppurative, cerebrospinal leptomeningitis and multiple brain abscesses. The lungs were each composed of three lobes and showed chronic passive hyyeremia but no pneumonia. There was no excess of fluid nor any adhesions in the pleural or abdominal cavities.

The heart weighed 70 grams and lay behind and to the right of the sternum in a position of detorsion. The pulmonary artery arose anteriorly and branched in the usual manner, the left branch being long and tortuous. The aorta arose posteriorly and to the right of the pulmonary artery. The aortic arch lay on the right side so that the innominate artery arose on the left side whereas the right common carotid and right subclavian arteries arose directly from the right-sided aortic arch. The ductus arteriosus arose from the aorta proximal to the left innominate artery and was attached to the pulmonary artery by a fibrous cord.

The coronary arteries were paired so that two ostia were present in each of the corresponding aortic sinuses. Both left coronary arteries were small and supplied the left side of the single ventricle. The two right coronary arteries diverged to either side of the right atrium and supplied the major portion of the musculature of the heart.

The heart was trilocular and biatriate. The atria communicated with the common ventricle by the usual orifices but a defect 1.7 cm. in diameter which lay anterior to and below the closed foramen ovale was found in the interatrial septum. The tricuspid valve lay in the right (venous) side of the heart and consisted of three well defined leaflets connected by chordae tendineae to a large papillary muscle in the right lateral portion of the ventricle. The mitral valve which lay in the left (arterial) side of the heart was rudimentary and consisted of two incompletely formed leaflets lying under a short membranous septum adjacent to the tricuspid valve and separating the origins of the aorta and pulmonary artery. The mitral chordae tendineae as they passed to a small papillary muscle on the left anterolateral wall of the ventricle interlaced with those of the tricuspid group.

The average thickness of the myocardium of the ventricle was 7 mm. The muscular portion of the interventricular septum was absent. The position of the smaller papillary muscle beneath the pulmonary and aortic orifices partially divided the common ventricle into a smaller left (arterial) and larger right (venous) portion, but these communicated freely. The pericardium and endocardium were thin, smooth and glistening.

The conus of the right side of the ventricle was stenotic below the pulmonary valve, its circumference measuring 2 cm. At the valve the circumference increased to 3.4 cm. There were only two pulmonic cusps, the third being replaced by a congenital ridge.

ABDOMINAL ORGANS. The left lobe of the liver was large and rounded containing most of the substance of the liver which weighed 380 Gm. The left leaf of the diaphragm was elevated over this portion of the liver. The gallbladder and biliary system were in the usual location. The spleen was absent congenitally. The portal vein was anterior to the pancreas and common bile duct. The kidneys and ureters, the stomach and jejunum, and the duodenum, had the usual locations and were of average structure. The ileum and cecum were not rotated and lay in the left lower quadrant attached by a long free mesentery.

The transverse colon and sigmoid lay in the right lower quadrant so that the rectosigmoid portion descended down the right side of the pelvis into the pelvic musculature. The right testicle was in the scrotum but the left testicle lay in the external inguinal canal.

The meninges were grayish yellow and thickened. There was a yellow, granular and friable exudate over the cerebral and spinal meninges. Cultures of the pleuropneumonia-like organisms were grown from this material. The cerebral ventricles were dilated and the left side showed evidence of previous hydrocephalus with recent inflammation.

DISCUSSION

Lichtman [1] in his extensive review has fully summarized the literature of dextrocardia and has indicated the need for further clinicopathologic reports. The intrinsic anomalies in the present case have made the study worthy of a review of the embryology of the heart [4] in an attempt to classify it under the groupings of Maude Abbott.[5] She cites a case reported by Mautner and Löwy [6] which is nearly comparable and lists it as an example of Spitzer's type II which is characterized by persistence of the right ventricular aorta, rudimentary interventricular septum (cor triloculare biatriatum) and stenotic bicuspid pulmonary valve. This heart differs in having paired coronary arteries and an interatrial septal defect in addition.

This heart has also been classified by Lichtman's criteria as "complicated dextrocardia" with "partial heterotaxia." He lists the following six types of complications found in dextrocardia with the heart in the present case having the first five.

1. Stenosis of the pulmonary conus
2. Auricular and ventricular septal defects
3. Trilocular biatriate chamber type
4. Venous anomalies
5. Anomalies of the valve ostia
6. Patent ductus arteriosus

The "uncomplicated" or "mirror image" type of dextrocardia does not have intrinsic anomalies. "Partial heterotaxia" in this case refers principally to the liver, portal vein, and large intestine.

Spitzer is quoted widely for the explanation of the ontogenesis of cardiac defects. Comparing the reptilian and human hearts, he based his theory [7] upon the clockwise torsion of the heart with fixed arteriovenous ends, combined with independent arrested development of the separate centers in the heart. Later, his [8] concept of "dextroversio" was to the effect that the characteristic factor is the inverse direction of the axis which is not the result of mirror picture architecture of the heart but of gross pathologic causes. The "detorsion effect," which this heart showed, is the absence of the 180° spiral rotation. It accounts for the partial or complete transposition of the aorta and pulmonary arteries. This case presented the persistent right aortic arch also explained in his theory on a mechanical basis.

Pernkopf [9] demonstrated that the asymmetry of the anlage of one organ does not influence an adjacent organ. Further he expressed the opinion that the different components of the embryonic heart may develop in an independent manner.

The present case illustrates the concepts of Spitzer and Pernkopf especially well since the viscera are not completely transposed. The influence of the heart and liver on the position of the diaphragm has been explained by Shapiro [10] and Roesler.[11] Also the lower position of the right testicle in cases of transposition has been noted by Ebstein, and Mandelstamm and Reinberg.[12]

Reid [4] also has made interesting observations on the cause and prevention of congenital heart disease. His paper gives further facts on the embryology of the heart. He attempts to explain the comparative rarity of monsters on the basis that great changes in the embryonal development of the heart leads to early abortion of such fetuses.

The author gratefully acknowledges the advice of Dr. Harold Feil in the preparation of the manuscript.

SUMMARY

A case of complicated dextrocardia with partial heterotaxia is described and compared with other reported cases. The possible mechanisms which may lead to this type of malformation are interpreted according to the theories of Spitzer and Pernkopf in the belief that they offer the best explanation of this case.

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DDT Tested Against Polio

Infantile paralysis gives signs of levelling off throughout the nation. At the same time a sharp outbreak in Wilmington, Del., has turned that city into a proving ground for DDT as an antipolio weapon.

A total of 529 cases for the nation were reported from state health officers to the U. S. Public Health Service for the week ending Aug. 23, latest on which official figures are available. This is an increase over the 411 reported the previous week. But it is only a 28 per cent increase, whereas there was 47 per cent increase during the preceding week (Aug. 16). The drop in percentage increase is what suggests that the polio season may be drawing to an end.

Delaware is having the largest amount of infantile paralysis for the size of its population, that is, the highest incidence rates, of any state. Latest figures for the state, obtained by special request of the U. S. Public Health Service to the state health officer, show that the state has had 78 cases from the first of the year through Aug. 25. Of these, 19 occurred on Aug. 22, 23, 24 and 25. Of the total since the first of the year, Wilmington has had the majority (57).

Wilmington has already had one spraying with DDT and will have another within a few days. The spraying, done from airplane and also by crews operating sprayers on the ground, is under the direction of Drs. Vernon B. Link and Griffith E. Quimby of the U. S. Public Health Service's Communicable Disease Center with headquarters in Atlanta, Ga.

Object of the spraying is to kill flies which are suspected of spreading infantile paralysis. Whether flies actually do spread the polio virus and whether, if so, they are the only means by which it spreads are two questions that have not yet been definitely answered.

If infantile paralysis cases drop off suddenly in Wilmington about two weeks from now, health authorities will feel that the case against flies is much stronger. They will not be convinced that flies spread the disease until they have had experience in eight or ten outbreaks in which cases drop sharply after flies have been routed.

Attempts to get evidence for or against flies as polio spreaders have been made with DDT before. One widely publicized was that in Rockford, Ill., in 1945. The fly population was reduced, but results on infantile paralysis were not conclusive. The reason was that the spraying was not done until the peak of the outbreak had been reached, so it was impossible to tell whether the drop in cases was due to the drop in flies or would have come anyway.

In Wilmington, the spraying has been started much earlier in the outbreak, so health authorities are hopeful that they will get more definite results. A drop in cases in less than two weeks would not be expected, because some will already have been infected before the spraying started. Ordinarily an outbreak would be expected to run for two months, so a drop in cases before then, especially a sharp drop, is the thing to watch for.

——From *Science News Letter*, Sept. 6, 1947.

Cases from the Medical Grand Rounds of the Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

CASES 23 AND 24

? RHEUMATOID ARTHRITIS

DR. MARIAN ROPES: These two cases we think represent an atypical form of a very common group of diseases. Dr. Elrick will present the first case.

DR. HAROLD ELRICK: Josephine S., No. 215708, is a 16-year-old white girl who came to this hospital on April 1, 1947 because of joint pain and fever. Two weeks before entry, she developed a dry cough, headache, and fever of about 101°. After two days of bed rest, she felt well enough to resume normal activity. However, six days before entry, the cough and fever recurred and, in addition, she developed generalized aches and pains, malaise, and over the course of the next six days her temperature ranged between 101° and 104°. Her local physician treated her for several days with a sulfa drug and 600,000 units of penicillin intramuscularly, without notable effect on her course.

On the day of entry, she noted the onset of pain in both elbows and the left knee joint, but there was no redness or swelling. There was no history of skin rash, dyspnea, or stiff neck, exposure to rodents or birds, or ingestion of any raw milk. The past and family history were entirely negative for joint or skin disease.

Physical examination on entry revealed her to be an acutely ill young girl, with a rectal temperature of 104°, pulse 120–130, respirations 24, and blood pressure 100/70. Her throat was diffusely but mildly inflamed, without exudate or edema. There were some pea-sized, tender nodes at the angles of her jaws. The heart was borderline in size with rapid, regular rhythm and no significant murmurs or friction rub. The extremities showed a very slight swelling of the left knee with some tenderness but no redness. The elbow joints were tender but not swollen or red. The skin was entirely clear. The chest was clear to percussion and auscultation. The abdomen showed no abnormal findings; the spleen was not palpable. Her initial urine showed 2 plus albumen and 2 plus acetone, but subsequently the urine has been entirely normal. Her hemoglobin was 11.5 Gm. Her initial white blood cell count was 20,000 with 90 per cent polymorphonuclear cells. Subsequent counts have ranged as high as 23,000 with as many as 93 per cent polymorphonuclear cells. Her throat culture was negative for beta hemolytic streptococci. A urine culture was negative. Three blood cultures taken at the height of her fever have not grown any organisms to date. Her electrocardiogram showed inverted T waves in the limb leads, as well as CF_2 and CF_4.

The temperature has ranged between normal and 106° by rectum, with a spike daily and occasionally a mild chill. On the seventh hospital day she developed a pleural friction rub as well as pleuritic pain in the left lower axilla. The rub disappeared within 12 hours but the intermittent pain persisted.

Everyone who has seen her has been struck by the contrast between her appearance and the temperature chart.

DR. ROPES: I think one of the most important things to show is that she really looks quite well in general. She does feel warm when she has fever and she surely doesn't feel entirely well, but, on the other hand, is not extremely ill as far as she is concerned. The one joint which was involved at the time of admission was the left knee, which now, I think, would be called negative or essentially negative. Those of us who saw it during the period when it did show definite swelling and thickening are still aware of the fact that it is a little larger than the right, but I am sure that it now would be passed as a normal joint by others. She shows nothing else on physical examination. The only glands palpable have been the anterior cervical and I think, one or two small posterior cervical nodes which are a little more prominent today. The spleen has not been palpable at any time.

She has had very slight left lower chest pain for the last few days. It was rather severe at the onset, at

which time a pleural rub was audible, but has been very slight for the past 48 hours.

DR. GEORGE REINBERG: May I say a few things? I saw her when she first became sick. There was nothing on physical examination to make any definite diagnosis. She had no pain in any of the joints. Her chest was perfectly clear. She had no rash. The throat was a little red. On the third day after I had seen her, her temperature came down to normal, and remained that way for 12 hours. Then at ten o'clock that night, it shot up to 104° and the next morning it remained at 104° and then went down to 103°. I saw no evidence of any rheumatic condition of the heart or lungs. It looked to me like a virus infection. I made no definite diagnosis and thought it best to have her admitted.

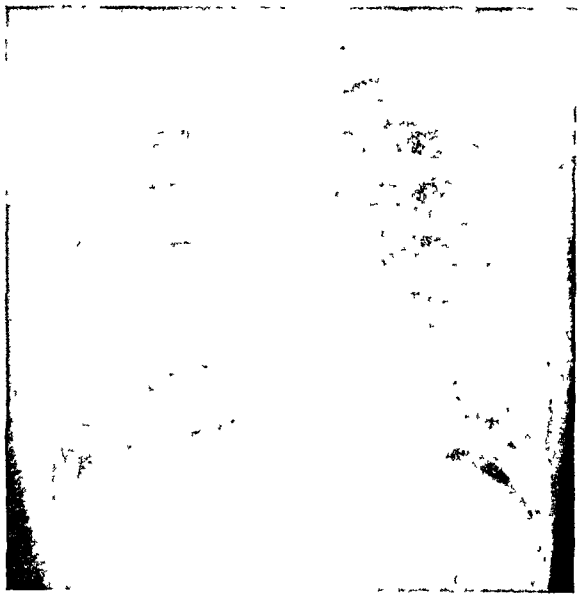


FIGURE 1

DR. ROPES: *I am very glad to have that additional* story, because that is consistent with the reason for which we are presenting her. In other words, she appeared to have at onset a severe generalized infection. Even at the time of admission our first impression was that we had to rule out some generalized severe infection. On the other hand, no bacterial evidence of any such infection has been obtainable and again I feel that with any of the known infections she would be a much sicker person today and would have more evidence of some localized process. As the time has passed, it has become more apparent that her disease probably belongs to the group of generalized connective tissue diseases, if we can describe them as such, in which are included rheumatic fever and rheumatoid arthritis. I think when one goes beyond that in this patient, it is very difficult to say which of these she has. I personally have favored rheumatoid arthritis because of several points. One point is important, namely, that with high fever she still looks relatively well and feels relatively well. That I think is unusual, if it ever occurs, in rheumatic fever. Also, the disease progressed steadily from the onset of the first symptoms. She had persistent swinging fever from the onset, which did remain down for periods of ten to twelve hours at a time, but has persistently swung up and down from the beginning, which again, is less usual in rheumatic fever.

The joint symptoms, on the other hand, are more in accord with rheumatic fever at the moment. They have been very transient in character. I think she now has a little more synovial thickening in the left knee than is usual in rheumatic fever of short duration, but I am sure that it is a minimal condition and not enough to be of diagnostic value.

To interpret the changes in her chest is also difficult. She has had minimal pulmonary involvement, if any. She has had pleurisy. We have none of the people from the x-ray department here, but they read this (Fig. 1) as a slight amount of fluid at the left base. There is a little more clouding of the pleural sinus on the left than on the other side, and there is one line which may or may not be identified with underlying involvement at the base. In any event, she surely has very little parenchymatous involvement, and I think a mild pleurisy of this type with development of a small amount of pleural effusion, again without much in the way of sickness, is more common in rheumatoid arthritis than rheumatic fever.

The entire picture seems to be consistent with this group of diseases in contrast to the generalized infection which was the first impression she gave.

Before I ask for any more discussion on her, it may be well to present the next patient, who we feel falls into the same group. Perhaps Dr. White would like to look at the cardiogram on the first patient, which is of interest in the same differential diagnosis. She has low T waves which I would assume to be consistent with pericarditis. This would be very common in either of these diseases, but once again the pericarditis of rheumatoid arthritis, in my experience, presents much less clinical evidence of cardiac involvement than does that of rheumatic fever. She has had a systolic murmur which was not, at most, more than of grade one in intensity.

DR. PAUL D. WHITE: I should think on the face of the course and the absence of cardiac enlargement and the electrocardiogram, that rheumatoid arthritis would be more likely than rheumatic fever. I don't know

that I have ever seen rheumatic fever producing pericarditis without some enlargement. Dr. Bland, have you?

DR. EDWARD F. BLAND: It would be most unusual.

DR. WHITE: The fact that the heart remains of normal size but the electrocardiogram is quite abnormal would favor rheumatoid arthritis.

DR. BLAND: Has she been on aspirin?

DR. ELRICK: 3.8 Gm. a day.

DR. WHITE: The P-R interval is normal, the T waves are abnormal. It is generally the other way around with rheumatic fever.

DR. ROPES: Perhaps we should now show the patient from the Pediatric Service.

DR. DAVID H. RIEGE: William McA., No. 567613, is a four-year-old boy who entered the ward on March 18, 1947. His chief complaint was fever of nine days' duration. He apparently had a normal birth and early development, and was well until the present illness. His family history is significant in that the mother had had rheumatoid arthritis.

The boy was well until ten days before admission, when a small reddened lesion on his right cheek was noted, which disappeared in 24 hours. Eight days before admission, the child awoke with a temperature of 103.2° and had a severe chill. He had six to eight loose bowel movements that day and vomited several times. Seven days before admission his fever was still high, around 102° or 103°, and a papular rash was noted over his trunk. Six days before admission he was put on sulfadiazine, which he received until the time of admission. The rash gradually disappeared, but the boy continued his febrile course, and three days before admission his left knee was found to be swollen and moderately tender, but not red. Also at this time the proximal interphalangeal joint of the left little finger was noted to be swollen, red, and tender.

The child was admitted to the hospital where he looked acutely ill, but was in no severe distress.

On physical examination he was found to have a generalized papular rash, the papules measuring about one half centimeter in diameter. His throat was moderately injected; there was no exudate or membrane. His heart was not enlarged, but there was a grade two systolic mitral murmur which was variable with respiration and position. His left knee was moderately swollen, tender, and warm. His left little finger was red, moderately swollen, tender, and his elbows were slightly tender. There was limitation of motion of the extremities involved. The laboratory data revealed normal urine and urine culture was negative. Two blood cultures were negative. His hemoglobin was 8.8 Gm., white blood cell count on admission 24,000, with 81 per cent polymorphonuclears. B. abortus agglutinations and Weil-Felix agglutinations were negative and an electrocardiogram was within normal limits with a P-R interval of 0.13 second.

The child had a febrile hospital course for the first two weeks. His temperature ranged from 99° in the morning to 101° almost every afternoon. He was placed on penicillin therapy for six days, and also received aspirin, 1½ Gm. a day for the first six days without effect on his course. These drugs were discontinued for about ten days and recently aspirin has been begun again. On the eighth hospital day, because of the persistent swelling in the left knee, a tap was done and about ten cubic centimeters of purulent material were removed containing 45,000 white cells per cubic millimeter and 89 per cent polymorphonuclears. The sugar content of this fluid was reported as 24 mg. per cent.

The child has received transfusions following which his hemoglobin has come up to 13 Gm.; he has been afebrile for the past nine days. The heart murmur is not audible at this time and it may have been due to the anemia. His left knee is still slightly swollen and tender, but he has regained most of the mobility of the joints that were involved.

DR. ROPES: In this patient, as the first, the thought on admission was that he also had a generalized infectious process. He already looks very much better than he did some three weeks ago. At the time of admission he objected considerably to having his elbows moved. They now move very readily without evidence of pain. He has had no recurrence of his rash. There is no question about the involvement of his left knee, with persistent effusion and thickening. He has, however, very little tenderness now. It was fairly tender at first and motion was very painful. I think he will move it with relative ease now; 70 degrees is as much as he will let us flex it at the moment.

Even when he had his fever, which at the start was not as high as in the other case and was persistent, he, too, did not look as sick as the average patient does with as severe a generalized infection as his chart indicated.

The original possibility from the point of view of an infection was, in our minds, Haverhill fever, due to the Streptobacillus moniliformis, and it was with this in mind particularly that we cultured the blood and joint fluid. The cultures were negative, not only for the Streptobacillus, but for any organism and there has been absolutely no evidence of bacterial infection.

The description here, as in the first case, gives evi-

dence that this patient's disease belongs to the same group of connective tissue diseases. In him, the differentiation beyond that stage is much easier, and I think that with this story one need consider only rheumatoid arthritis. There is nothing to suggest rheumatic fever. The joint involvement with the persistent thickening and effusion would be very much against it. The joint involvement, on the other hand, is entirely consistent with rheumatoid arthritis.

At this stage, if Dr. Bauer would talk or comment on these two patients and the group of diseases to which they belong, we would be glad to hear him.

DR. WALTER BAUER: I have very little to add to what Dr. Ropes has said already. It is perfectly evident that, lacking specific diagnostic tests, such diagnostic problems will arise repeatedly: Does this patient have a specific infectious disease or is she suffering from one of the connective tissue diseases? At the moment all we can do is observe and record the clinical findings and hope that with the passage of time we can make the correct diagnosis. If this patient had an eosinophilia of 20 per cent, we naturally would think of one of the diseases closely allied to rheumatic fever and rheumatoid arthritis, namely, periarteritis nodosa. Or if the patient gave a history of having had an erythematous, butterfly rash, extending over the malar prominences with or without certain urinary findings, one might entertain the diagnosis of disseminated lupus erythematosis. I believe the first patient probably has rheumatoid arthritis; however, I have no way of proving it. One could argue that certain of these findings are also consistent with the diagnosis of rheumatic fever. That is correct. We have seen a few cases of rheumatic fever, exhibiting objective joint signs and limitation of motion for weeks, occasionally for months, who developed mitral stenotic murmurs while under observation. Later the joint findings disappeared and never reappeared.

DR. WHITE: How about a coincidence of the two conditions?

DR. BAUER: That is even more difficult. We have seen such combinations. The best example we had was eight or ten years ago: A colored woman who, everyone agreed, had both diseases. She died and unfortunately we were unable to obtain an autopsy. Because of certain clinical and pathologic findings, we wish we knew more about cardiac involvement in rheumatoid arthritis. Pericarditis has long been recognized. We have had several patients in whom at autopsy, we were able to demonstrate typical rheumatoid nodules in the pericardium.

DR. WHITE: Myocarditis may also appear.

DR. BAUER: We do see myocardial lesions but our present methods of examination do not permit us to say they are due to rheumatoid arthritis. Three of our rheumatoid arthritics had aortitis. However, none of the pathologists would make a diagnosis; they would only say that in no instance was it due to syphilis or rheumatic fever. Was the aortitis a manifestation of rheumatoid arthritis? If we are truthful, we must say we do not know. However, if one observes several rheumatoid arthritics develop pericarditis and subsequently aortic regurgitation during exacerbations of their disease, one asks, does rheumatoid arthritis affect the heart? Can it produce valvular heart disease? The pathologic evidence to date suggests that rheumatoid arthritis and these allied diseases are systemic diseases in which connective tissue is affected. We think it is the connective tissue rich in mucin. Our next job is to try to obtain a better definition of the receptors, first in the normal, and then try to relate that in terms of disease as our knowledge accumulates.

DR. F. DENNETTE ADAMS: Dr. Ropes, may I ask a question? You did consider meningococcemia, especially in the second patient, and perhaps in the first?

DR. ROPES: We did very definitely in the second. In the first, we did not very seriously, because there was little to point towards it in the way of suggestive symptoms. With rash, arthritis and generalized infection, we considered it in the second case, however. The rash would have been extremely unlike the usual meningococcus rash, but that was one of the conditions we wanted to rule out by taking the blood culture.

DR. ADAMS: The rash was maculopapular?

DR. ROPES: There was a diffuse erythematous rash on the face originally and varying types of lesions over the body, some of them papular, which could have been considered comparable to that of meningococcemia, but showed more variation than is usually seen. It was a possibility and one which was mentioned when we first saw him.

DR. ADAMS: Is the white count perfectly consistent with the diagnosis?

DR. ROPES: This particular group that has the high fever, which we sometimes refer to as the constitutional type of rheumatoid arthritis, does tend to have a very high white count. In a few occasions it is low, but more commonly in rheumatoid arthritis of this type it runs from 15,000 to 40,000 in the blood and in the joint fluid is comparably very high, as in the second case with 45,000 cells per cu. mm. A laboratory finding of interest in the second case was the 3.4 Gm.

concentration of globulin which, in our experience, is somewhat unusual at that stage of the disease.

DR. BAUER: Dr. Blackfan was the first one to call this maculopapular rash to my attention. In youngsters with so-called Still's disease it may be present for only a matter of minutes or hours. The maculopapular rash that this youngster displayed is much more frequent in children than in adults. I have a youngster of 12 in the private pavillion who has been having a leukocytosis as high as 50,000 for twelve months. She has never had any complicating infection, and the articular manifestations are mild in nature.

DR. ROPES: In fact, this group in general tends to have milder articular manifestations and usually somewhat less residual than the group which starts with chronic joint involvement.

DR. LEWIS K. DAHL: I would like to ask Dr. Bland if the failure to respond to aspirin would be a fairly strong argument against rheumatic fever?

DR. BLAND: Fairly strong. There are just enough exceptions I think, when you find yourself dealing with one case, to make you somewhat uncertain.

A PHYSICIAN: Have you accounted for the fever being present for so long a time before the joint symptoms?

DR. ROPES: I have no explanation but we know that it happens. We have seen some patients in whom the fever was present for months before the joint symptoms appeared. During that period, it was impossible to make a diagnosis but in retrospect we assumed those months were a phase of the disease, which turned out to be rheumatoid arthritis. One patient had 18 months of fever before she had joint involvement.

DR. BAUER: I think it is another way of saying that the fever is a manifestation of the constitutional disease. During this period they may have other symptoms: weakness, marked weight loss, and yet have no articular manifestations. At the Children's Hospital, one notes that certain children following the first attack of the disease were discharged with a diagnosis of "fever of unknown origin." In the subsequent attacks the articular manifestations became evident; in retrospect one is led to believe that the first febrile period was the initial manifestation of rheumatoid arthritis.

A PHYSICIAN: Has the possibility of a Bacteroides infection been considered here? I think the young man had diarrhea at some time.

DR. ROPES: Yes. Bacteriologically it has not been found, but one might think of it. But most of those patients are extremely ill. When they have this degree of fever they are extremely sick and usually the joint involvement is more severe than in the second patient.

Follow-up Two Weeks Later

DR. ROPES: The four-year-old boy has continued to improve; he has continued free of fever, has no joint symptoms, has only slight swelling of his knee and is almost well.

The 16-year-old girl went steadily down hill from the time she was seen here two weeks ago. She continued to spike a fever daily, ranging from 103° to 106.6°. On the day after she was seen here, she developed rather severe pain and tenderness of all the muscles of her legs. On the next day she developed a diffuse maculopapular rash, and, on the day following that, she developed the complication of salicylate toxicity as evidenced by hyperpnea. She was found to have a very low CO_2 of 9.1 m.eq./l. and the pH was actually on the acid side of normal (7.35). The following day she was noted to be jaundiced and the jaundice progressed steadily to the time of death. Her muscle pains and tenderness persisted but she had no more joint symptoms.

She died on April 17 and at autopsy the significant findings were, in the first place, an adherent pericarditis, which interestingly enough, seemed to be of more than four weeks' duration. The total period of apparent illness had been approximately four weeks, yet this pericarditis was of more than four weeks' duration, as I think Dr. Castleman will agree. There was evidence of pleuritis on both sides with adhesions extending over two-thirds of the chest on the left and over half on the right.

The liver was brownish-yellow, somewhat enlarged and soft, and, on histologic examination, showed focal necrosis. The spleen was enlarged. There were submucosal hemorrhages in the gastro-intestinal tract and petechial hemorrhages in the skin.

I might say that she had bled from the nasopharynx and gastro-intestinal tract during the last three days of life. The prothrombin time was elevated to 35 seconds at the time salicylate toxicity became apparent, and then appeared to fall, although not with good clotting. It then rose again to infinity.

The diagnosis of the underlying disease remains unknown. I think the most likely diagnosis is one of the generalized connective tissue diseases resembling rheumatoid arthritis and disseminated lupus erythematosus.

CASE 25

? THIOURACIL POISONING

DR. HELEN S. PITTMAN: We are going to show a woman who came to the hospital with hyperthyroid-

ism, who was started on treatment and who has displayed what we believe to be manifestations of thiouracil toxicity. We think this is an important subject. Dr. Freymann will present the history of the patient.

DR. JOHN FREYMANN: Mrs. B., No. 551817, is a 25-year-old mother of two children who was admitted to this hospital on April 7, 1947 with a diagnosis of thyrotoxicosis.

Her history is short and typical of this disease. Two years ago she gave birth to a deformed child after difficult labor. Over the ensuing year and a half she had a great deal of domestic difficulty. During this time she began to notice nervousness and great irritability. About six months ago she noticed prominence of her eyes. Her local physician suggested she have a B.M.R. taken, and this was found to be plus 60. She refused medical treatment at that time.

In the six months preceding admission she noticed increasing appetite, in spite of which she had lost about 45 pounds. About four months ago she noticed that she had a mass in her neck. Her periods had become sparse and she had had occasional bouts of mild diarrhea.

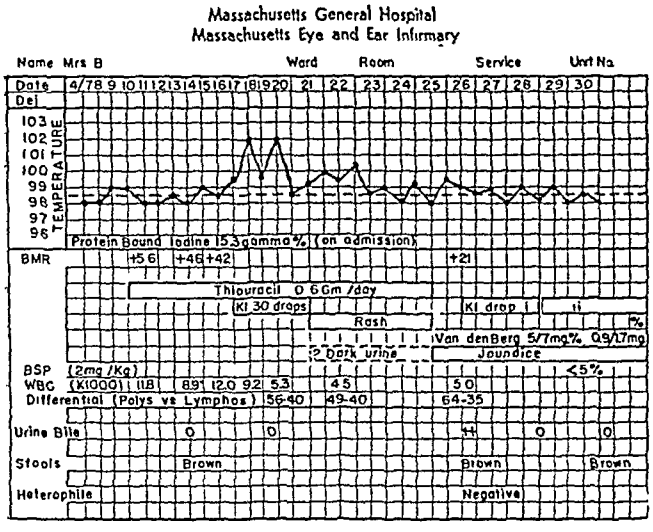


FIGURE 2

On admission to the hospital she was found to be a well-developed, very active woman, who was jumping around in bed. She had a sweaty skin, tremor of the hands, prominent eyes, but no lid lag. Her thyroid was 2½ times normal size, symmetrical and without nodules; there was a bruit heard over the gland. There was a grade two systolic murmur heard along the left sternal border. The liver and spleen were not felt.

Her white blood cell count was 6,600 with 65 per cent polymorphonuclears, 35 per cent lymphocytes. Her hemoglobin was 12.5 Gm. Her B.M.R. was plus 60 on admission; her serum protein bound iodine was 15.3 gamma per cent (normal 4–8 gamma per cent).

After three days in the hospital she was started on thiouracil 0.2 Gm. every eight hours. On the evening of the eighth day she received ten drops of potassium iodide. On the next day she received 30 drops. The order was ten drops three times a day. On the evening of the ninth day her temperature began to rise, and on the tenth day rose to 102°, as indicated in Figure 2. The patient complained of malaise and four large postauricular lymph nodes were palpable. There was conjunctivitis, but no definite rash could be made out.

The differential diagnosis was considered to be between German measles and iodism. At that time her white count was 5,300 with a differential of 56 polymorphonuclears and 40 lymphocytes. Because of the possibility of German measles, she was sent to the isolation ward. Iodide was stopped on the following morning. Throughout the next three days, her temperature went to 102° every afternoon and evening. She had considerable malaise with the fever, but otherwise felt well. On the afternoon of the tenth day, a small, very faint rash appeared on the forehead. This increased and spread over the face, the trunk and arms, and reached its greatest extent on the morning of the 13th hospital day, when it rapidly disappeared; at its height, it had a morbilliform character. By the time the rash had disappeared, her temperature had come back to normal and she felt quite well. All this time, thiouracil was being continued.

On the afternoon of the 13th day of thiouracil, she became anorexic. On the following morning, the sight of her breakfast made her vomit. Upon examination at this time she was noticed to be quite definitely jaundiced; that had not been noticed before, although she had been thoroughly examined. On further questioning, however, we found that she thought that her urine had been dark and her stools light since the day she had been put in the isolation ward, that is, the tenth day on thiouracil. Unfortunately, no urine or stools had been done in those four days. A Van den Berg taken as soon as she was found to be jaundiced was 5 mg. per cent direct and 7.2 mg. per cent total. Her urine showed 2 plus bile, and stools contained bile and bilirubin.

Thiouracil was stopped immediately following which the urine became bile free by April 28. Her appetite returned and she felt well. The jaundice has decreased; yesterday the Van den Berg was 0.9 mg. per cent direct and 1.7 mg. per cent total. A bromsulfalein test made with 2 mg. per kilo showed less than five per cent retention. A heterophile agglutina-

tion test on the first day jaundice was noticed was negative.

Two days ago potassium iodide was started again, first one drop, then two daily, and she has had no reaction to that. Her last B.M.R., taken on the 20th day, that is five days after thiouracil was stopped, was plus 21.

DR. PITTMAN: This, perhaps, is clearer now than it was to us at the time. The first manifestations of toxicity coincided so very closely with the beginning of the administration of potassium iodide that we blamed the rash on the iodide and stopped it immediately. It was not until we observed her a little longer that we directed our attention toward what else might be giving her the symptoms.

She is looking pretty normal in color, I think. The sclerae look pretty clear. There is perhaps a slight stare, but no lid lag at the moment. The thyroid is moderately enlarged and firm.

Would you like to see her, Dr. Means?

DR. JAMES H. MEANS: I saw her a day or two ago.

DR. PITTMAN: Dr. Munroe, the fourth year medical student who did the work-up on Mrs. B., has reviewed the literature on thiouracil toxicity. He reported it to us on rounds a couple of days ago, and I thought it was interesting enough to ask him if he would repeat it for us this morning.

DR. JOHN H. MUNROE: Most of the literature in the last couple of years on the toxicity of thiouracil has dealt largely with leukopenia and agranulocytosis, which occur as the two major toxic manifestations of thiouracil, although a large number of toxic reactions have been observed. The others include edema of the legs, nausea, diarrhea, jaundice, urticaria, maculopapular rash, Mikulicz's syndrome, psychoses, hematuria, and unusual sensitivity to opiates. Dr. Robert Williams [1] at the City Hospital has reported 247 cases and the toxic manifestations found in that series. Also, he reviews the literature of 793 cases. In the latter series of cases he found 4.8 per cent of leukopenia and 0.6 per cent of agranulocytosis; of this 0.6 per cent (five patients) three died. At the City Hospital there were three cases, with no deaths. But this was later when they understood thiouracil a little better. They treated the agranulocytosis with pentnucleotide, liver extract, pyridoxine, sulfadiazine, and penicillin.

Dr. Williams reviewed the factors involved and found that age was not of much significance in the occurrence of toxic manifestations. The ages ranged from 15 to 72 years and the average was 46; but of the fatal cases, three were over 50 years. Toxicity is four times as frequent in females as in males, but thyrotoxicosis is approximately four times as frequent in females as in males. The general condition of the patient was found to be a large factor. Apparently, poorly controlled diabetes, emaciation, and debility were directly responsible or related in two cases of fatal agranulocytosis. Other sensitivity phenomena such as sensitivity to phenobarbital or iodine played a large part, and four cases showed a sensitivity to iodine after thiouracil had been stopped because of a skin rash.

The dosage in one half of the cases of agranulocytosis was 1 Gm. a day which is now considered excessive. The toxic reactions usually occurred with larger doses, but thiouracil concentration in the blood stream was not found to be higher in the toxic reactors than in those who did not show toxicity. Duration of treatment was found to be important, and treatment over a long period of time was much more dangerous if it was intermittent. Of 250 cases treated, there were only 7.2 per cent in whom the drug had to be stopped completely.

Thiouracil is not a protein itself, but it acts by combining with the protein. It is thought [1] that it can thus produce a typical anaphylactic reaction. One case was reported [2] in which a good liver biopsy was obtained. The woman was on outpatient treatment with thiouracil when she developed jaundice, but she had been ill for a week and continued on thiouracil before she was brought to their attention. Her blood studies seemed to indicate an obstructive type of jaundice and a laparotomy was performed. The liver was shrunken and had a greenish tint. A biopsy of the liver was done and the report was "acute bile stasis." The patient's jaundice disappeared after laparotomy and after stopping thiouracil. Readministration of a test dose of the drug caused toxic symptoms of pruritis, diarrhea, nausea, and vomiting. The thyrotoxicosis was subsequently cured by surgery, preceded by preparation with iodine.

Dr. Moore [3] sent questionnaires to clinics in this country and in England and got a report on 1,091 cases. Seven-tenths per cent was the total death rate in this group. There were 0.7 per cent deaths during periods of treatment, but only 0.46 per cent were attributable to the drug. All of these were from agranulocytosis. He found that agranulocytosis usually oc-

[1] R. H. Williams, H. M. Clute, T. J. Anglem, and F. R. Kenney: Thiouracil treatment of thyrotoxicosis, J. C. Endocrin., 6: 23–51, 1946.

[2] S. L. Gargill and M. F. Lesses: Toxic reactions to thiouracil, J. A. M. A., 127:890–898, 1945.

[3] F. D. Moore: Toxic manifestation of thiouracil therapy, J. A. M. A., 130:315, 1947.

curred within the fourth to eighth week of thiouracil therapy, but was reported as early as the second week and as late as the 36th week. Febrile reactions, skin rashes, jaundice, and other minor manifestations usually occurred within the first three weeks, predominantly from the ninth to the eighteenth day.[4] These reactions, with the exception of agranulocytosis, seemed to disappear on removal of the drug; jaundice disappeared without treatment, other than supportive therapy, just as if it were infectious hepatitis.

DR. MAURICE FREMONT-SMITH: Didn't the Mayo Clinic report a few cases of encephalitis following thiouracil?

DR. RULON W. RAWSON: A few cases. I am not sure that they have proved adequately that it was due to thiouracil.

DR. PITTMAN: This woman presented in sequence fever, rash, and then jaundice, and because these started almost immediately after the addition of iodide, we withdrew the iodide first. It was not until the development of jaundice that we suspected for the first time that the thiouracil was at fault.

Dr. Means, would you like to say anything about this?

DR. MEANS: I think it is a very interesting problem. The diagnosis of what happened to her is important and also the therapeutic program is very important in view of the complications. I would agree with you in retrospect that the rash was not due to iodine. I think the iodine probably had nothing to do with this picture. That would be my general impression. Iodine will give rashes but they are usually not of the kind that was described here. I did not actually see this rash. Iodine will give involvement of the salivary glands sometimes, a sort of iodine mumps picture, but I think it is much more likely that thiouracil is responsible for all that went on here; that it was some kind of allergic response to that drug.

We have seen a case something like it. We have certainly seen an impressive lymphadenopathy in one case and various sorts of rashes, and we have seen fevers. This could be a drug fever, I suppose, even though it cleared up while she was still on the drug. We used to prove drug fevers, when there were not other complications, by exhibiting the drug and seeing whether the fever returned. In view of the involvement of the liver here, that would be undesirable.

One also has to consider, I suppose, the possibility that this had nothing to do with the drug, and that she has some kind of intercurrent infection, a mild hepatitis of other origin, and we would like very much to know what the liver experts think about that possibility. With regard to lymphadenitis we must try to decide whether she had anything in the way of intercurrent infection that could have produced it. I think that point has to be cleared up.

Now, if it turns out that this picture is due to drugs, we have to figure out how we are going to treat her Graves' disease. She was responding nicely to the drug except for this untoward side effect, apparently. It seems to be clear that we cannot go on with thiouracil. I don't know any way of finding out whether one of its chemical relations, like propylthiouracil, could be tolerated by her or not, except by trying it. Propylthiouracil apparently is less toxic than thiouracil.

Then there is the question of whether she could be prepared for thyroidectomy by means of iodine alone. I have no doubt she could be. In fact, I feel quite confident she could. Because, after all, until the antithyroid drugs appeared on the scene, we prepared all patients that way very satisfactorily, although not quite as satisfactorily as we do now.

But it is not as simple as that, because of this liver complication which she has had. Does that constitute a contraindication to doing any kind of surgery in the near future? I would like to know what Dr. Jones thinks about that. I frankly don't know. I am sure that doing abdominal surgery to her directly after a hepatic process of this kind would be undesirable, but whether a thyroidectomy under, perhaps, local anesthesia, would be inadvisable I don't know. I would think it perhaps could be done with safety, in about two weeks.

Then there is the matter of whether we should treat her with radioactive iodine. The difficulty about that is that she is young; that we don't know the later untoward effects; that it is slow acting. I think that you would like to control her thyrotoxicosis reasonably soon because, after all, thyrotoxicosis is not good for the liver. Indeed, in the past, there has been a certain amount of literature describing liver lesions resulting from thyrotoxicosis itself. So that I would like to get her over her thyrotoxicosis. I would end my discussion by putting it up to those who know more about liver disease than I do. How dangerous would it be to thyroidectomize her, after iodine preparation, in say two or three weeks' time?

DR. PITTMAN: It is for that reason that we have asked Dr. Jones to come here.

DR. CHESTER M. JONES: How long, Dr. Means, do you think it would take from the present date to have

[4] J. W. McArthur, R. W. Rawson, and J. H. Means: Idiosyncratic febrile reactions to thiouracil: clinical characteristics and possible pharmacologic significance, Ann. Int. Med., 23:915–923 (Dec.) 1945.

her prepared adequately with iodine, other things being equal, forgetting the liver for the moment?

DR. MEANS: What was the last B.M.R.?

DR. PITTMAN: Yesterday it was plus 21.

DR. MEANS: You know, the surgeons, since the advent of antithyroid drugs, have gone perfectionist about the preparation for operation. In the old days they oftentimes said a plus 20 B.M.R. was perfectly good enough preparation, and they went ahead and got away with it. Now they think that is not by any means a good enough preparation. I should think two or three weeks more on iodine alone should get her in a state where a surgeon who is really expert in doing thyroid surgery could get her through it.

I wish you would call on Dr. Rawson before you get through, because I believe he thinks I am a little too much of an optimist about this situation. At any rate, I would like to have him express his point of view about the operative risk here when Dr. Jones gets through.

DR. JONES: I am glad you expressed yourself the way you did, because it seems to me it is simply throwing away previous experience to be too pessimistic about a situation like this, as far as the perfection of preparation is concerned. In the first place, I don't think this patient had infectious hepatitis. Most patients with infectious hepatitis with a temperature as high as 102° would have had a longer lag before they developed clinical jaundice. In other words, the existence of a high temperature in relation to the time of spilling over of bilirubin is a little too close to be anything but a rather unusual occurrence for infectious hepatitis. I admit it could be, but I don't think it is.

DR. WALTER BAUER: How can you say that did not take place four to six weeks ago and this is the temperature which precedes the actual onset of jaundice, which we sometimes see?

DR. JONES: You can't, but it is unusual, because 102° is a real elevation of temperature, and I take it that this persisted for five days or more, while clinical jaundice was developing steadily. The very fact that one week after the clinical jaundice appeared she had only 5 per cent bromsulfalein retention would seem to indicate the amount of liver damage was very small. I think that in itself is a pretty good indication of the degree of damage. Furthermore, her jaundice has diminished from 7.0 mg. per cent total bilirubin to 1.5 mg. per cent. In other words, the clinical and laboratory demonstration of jaundice has been one of rapid improvement. So I would think the amount of liver damage was relatively little. If you could take two weeks or two weeks and a half to get a proper iodine preparation for operation, I believe the liver would be in perfectly good condition to stand thyroidectomy at that time.

It is true that Dr. Beecher has shown, for example, that a deterioration of liver function in otherwise normal livers follows a general anesthesia. That is not new. We have seen that frequently over the years. And where there is some liver damage, then a general anesthetic over any length of time, three or four hours, produces fairly striking changes in liver function, with a recurrence of jaundice at times. But I would think that under ordinary circumstances the operation here would be a relatively short one, probably not more than an hour and a quarter, or an hour and a half. Isn't that so?

DR. MEANS: It could be done under local anesthesia.

DR. JONES: Why not plan to do it under local, when everything is normal from the point of view of hepatic function? I would repeat the liver function tests in two weeks' time and I would do several tests. I would do the bromsulfalein test surely, using a 5 mg./kg. dose instead of 2 mg./kg., and see whether there is more than 5 per cent retention. If there is, we have to be more careful. I think I would do a cephalin flocculation test, and I am sure I would test the prothrombin. That ought to be done now. I should think she would be a perfectly good risk with a little more preparation.

DR. PITTMAN: The cephalin flocculation is plus-minus and the prothrombin test has not been done.

Dr. Rawson, do you want to say anything before we turn this meeting over?

DR. RAWSON: If the fever is due to thiouracil, it is the first one we have seen in this hospital which subsided on continuation of the drug. Otherwise, I think the picture could be due to a toxic effect of thiouracil. I was glad to hear what Dr. Jones had to say, because I was not willing to take the risk of going ahead with an operation until the liver experts had given their opinion. If he feels she would tolerate it, that is fine. I think, as he suggested, that liver function tests should be done again in a couple of weeks before she is subjected to that procedure, and then I would consider local anesthesia.

DR. MEANS: I would not worry about the potassium iodide. You are giving her two drops only. You don't need to give her as much as 30; that was too much, and two drops is too little. I would put her on five or ten a day.

There is one question I would like Dr. Rawson to answer, and that is, with regard to a situation of this kind, how would he feel about shifting to propylthiouracil and giving that a trial?

DR. RAWSON: I would be reluctant to do it. We

don't know enough about the toxic effects. We do know that propylthiouracil has less effect on the hematopoietic system.

There is one other thing. I think Dr. Pittman said they were using homeopathic doses of potassium iodide. Two drops of potassium iodide is equal to 120 mg. You are giving her 2 Gm. with 30 drops, which is quite pharmacologic.

DR. BAUER: Do you think we can say for sure that this was a thiouracil reaction?

DR. RAWSON: I am not willing to accept this unequivocally as a thiouracil reaction, because the fever subsided while taking the drug.

DR. MEANS: If it is an iodine reaction you will get fever on giving iodine again.

DR. RAWSON: You should have had it before, yes.

Editor's Follow-up Note

This patient continued to improve both clinically and by laboratory examination after she was presented at Grand Rounds. She was maintained on a high-protein, high-carbohydrate diet and on the 13th of May she had a bilateral subtotal thyroidectomy under gas-oxygen-ether anesthesia without difficulty. Postoperatively she developed mild tetany which cleared gradually and she was subjectively well on the 24th of May when she signed out against advice.

When she was seen on her first follow-up visit on the 4th of June she was subjectively well except for mild tingling in the feet in the mornings associated with carpopedal spasms. On this date her serum calcium was 7.2 mg. per cent and her phosphorus 4.1 mg. per cent. This visit was made to the Surgical Outpatient Follow-up Clinic, where no mention was made of the status of the liver, but since her liver function studies were normal pre-operatively, and she had no symptoms referable to the gastro-intestinal tract postoperatively, it is assumed that liver function was normal. She will be seen in the Medical Outpatient Clinic for further follow-up.

Inventory of the Nations Sanitation Needs

More than 100 million Americans need improved water supplies and waste disposal facilities according to a nationwide inventory of sanitation needs recently made public by the Sanitary Engineering Division of the U. S. Public Health Service.

The cost of remedying this condition is estimated at $7,834,581,000. This represents a minimum sum that should be spent to reduce the incidence or potential incidence of filth-borne diseases such as dysentery, diarrhea, and typhoid fever.

Health departments of every state, as well as hundreds of county and city health departments, co-operated with the Public Health Service in making this the most complete inventory of basic sanitation needs ever compiled for the nation. It itemizes, state by state, the cost of obtaining the healthy environment essential to a national health program.

Results show that, on the basis of June 1946 costs, the nation needs 2.2 billion dollars worth of water works construction to serve more than 81 million persons in towns and cities. Sewerage facilities needed by 85 million persons in communities of over 200 population will cost approximately 3.7 billion dollars. Cost of needed garbage collection and disposal facilities is estimated at 166 million dollars. It will cost approximately 1.6 dollars to provide decent sanitation for the 27 million persons living in rural homes with unsatisfactory water supplies and for the 33 million rural residents who lack adequate waste disposal facilities.

Almost 40 per cent of this needed construction is at least at the planning stage, according to the survey. Over nine per cent of needed sewerage facilities, costing approximately $360,509,000 is ready for construction now and an additional 24 per cent, costing $908,048,000 is definitely planned. Almost 17 per cent of the needed water supply systems, costing $381,829,000 is ready for immediate construction and plans are in progress for an additional 27 per cent costing $612,111,000.

The per capita cost of needs is greater in the smallest communities and in the largest. In towns of less than 1,000 population, needs exceed $100 per capita, while in cities of over 100,000 population, needs are over $80 per capita. In towns of intermediate size, the per capita cost is about $50 and in rural areas about $40.

Cost estimates take into account variations in economic status and in practices and policies of local communities.

There is no more important problem facing the medical profession today than the need to diagnose cancer at the earliest possible stage. This is a direct responsibility of the individual doctor and one which he must discharge satisfactorily if he is to justify the present confidence placed in him by the public. Failure to do so is the more reprehensible when, as occurs so often, it results from neglect of simple examinations available to all.

Carcinoma of the Rectum and Anus*

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Although the diagnosis of carcinoma of the rectum or anus can be easily and accurately made when the lesion is suspected, it is a disturbing fact that most of the patients, when first seen by a surgeon, have far advanced malignant disease. Too often indeed, the patient disregards his symptoms for several months before seeking medical advice. On the other hand, in some cases, an unsuspecting physician will treat his patient for a benign lesion simply because his examination has been inadequate. Considerable progress has been made during the past decade in the preoperative preparation, surgery and postoperative management of these cases, but a remarkable improvement in the five-year-survival rate will not occur until these patients are brought to surgery in an earlier stage of this disease.

Carcinoma of the rectum and anus accounts for approximately five per cent of all deaths from malignant lesions. Of 3,542 malignancies of the large intestine operated upon at the Mayo Clinic between 1907 and 1928, 2,259 or 63.48 per cent were distal to the sigmoid colon.[1] Neoplastic disease of the lower bowel is approximately twice as frequent in males as in females; in a group of cases recently reviewed, 75 per cent of the patients were males and 25 per cent were females. Most of the patients are between 50 and 70 years of age; nevertheless, one must not lose sight of the fact that between one and five per cent of those affected are below the age of 30.

ETIOLOGY

It is now generally accepted that certain benign lesions of the rectum, namely, single or multiple polyps and adenomas, must be considered as precursors of carcinoma. Especially is this true when polyps in the rectum are part of the picture of congenital familial polyposis involving the entire large bowel. If these patients live long enough, and remain untreated, they will invariably develop carcinoma. It is known that rectal polyps are quite common, as shown by Hayes and Burr,[2] who, during routine proctoscopic examination over a seven and a half year period, discovered 185 rectal polyps, most of them asymptomatic. Numerous reports have appeared in the literature concerning these lesions in which pathologic examination postoperatively has revealed the presence of malignant degeneration in scattered areas of the bowel with benign polyps intervening. One is by no means justified in assuming that all malignancies of the rectum arise from benign lesions, but there is some evidence to support that theory and malignant degeneration of benign rectal lesions has been observed frequently enough to be considered a common occurrence.

There is some difference of opinion concerning the role of inflammatory disease of the rectum as a precursor of carcinoma. Rankin [1] feels that even though the incidence of rectal carcinoma arising in lesions such as hemorrhoids, ulcerative proctitis, anal fissure and strictures is low, it is reported often enough to make it important in any consideration of the etiology of rectal malignancy. The consensus, however, is that these lesions occur in the presence of carcinoma rarely enough to be considered coincidental or secondary. Parasitic infestation and constipation are of little significance as etiologic agents. If constipation were an important factor, it would make itself evident by a high incidence of anal carcinoma, the anus being the portion of the lower bowel most exposed to the irritation of the fecal stream. Such an incidence is not shown statistically.

PATHOLOGY

Rectum. Carcinomas of the rectum are most common in the rectosigmoid area and decrease in inci-

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dence from that point distally. They invariably arise from the glands of Lieberkühn and are therefore all adenocarcinomas histopathologically. Various clinical classifications have been used to designate the various forms, such as the papillary, scirrhous, nodular and colloid types, but Broder's classification into Grades 1, 2, 3 and 4 on the basis of cell differentiation microscopically is of more prognostic value. Grade 1 is defined as a tumor in which undifferentiated cells represent only 1 to 25 per cent of the total epithelium; Grade 2, 25 to 50 per cent; Grade 3, 50 to 75 per cent; and Grade 4, one in which 75 to 100 per cent of the epithelium is undifferentiated, or "out of control." Fortunately, approximately 75 per cent of rectal carcinomas fall into Grades 1 and 2 of Broder's classification. Closely paralleling this latter method, in determining prognosis, is the determination of the number of mucus-secreting cells in the sections, as originated by Ochsenhirt. As the mucus-secreting cells represent an attempt at differentiation by the tumor, into the type of cell from which it arose, the amount of mucus present has been shown to be inversely proportional to the grade of malignancy.

In general, carcinoma of the rectum can be considered to be a slow growing tumor, as shown by the frequency with which a completely encircling or "napkin-ring" type of growth can be demonstrated without evidence of metastatic disease. The site of origin, as previously stated, is in the mucosa, and undoubtedly the tumor may be confined to the mucosa and submucosa for a considerable period of time before ulceration occurs and the typical raised, indurated, nodular edge of rectal adenocarcinoma is formed. The invasion of the circular muscle layer is also late and it is not until this layer has been traversed, and the intermuscular lymphatic network is invaded, that encirclement of the rectum, to form the common type of obstructing rectal carcinoma, begins. The longitudinal muscle layer is next in the line of direct extension and after its involvement the tumor tends to be temporarily limited by the rectal fascia.

Local Invasion. Depending upon the site of the original tumor in the rectum, various surrounding structures are commonly invaded by the continued local growth, and interruption in the continuity of the rectal fascia. Most commonly involved in this manner are the prostate, bladder, uterus, vagina, presacral fascia and the lateral walls of the pelvis. It has been pointed out recently by Lahey [3] that only the latter type of direct extension, that is, fixation of the rectum laterally, should be considered truly inoperable, in the absence of distant metastasis, unless involvement of the organs mentioned is very extensive.

Metastasis. Carcinoma of the rectum fortunately tends to remain localized for a long period of time, but when metastases finally do occur, they are almost invariably first demonstrable in the retroperitoneal lymph glands. The normal course of further extension is upward, as pointed out by Glover and Waugh,[4] who state that "It has been demonstrated that even in cases of far advanced carcinoma in this region, retrograde spread along the course of the bowel occurs to any degree in only 1 per cent. When such retrograde spread can be demonstrated, it is an indication that upward normal channels have been blocked."

The invasion of venous channels accounts for the frequency of hepatic involvement through the portal vein without evidence of any other distant metastases. The importance of vein invasion, found microscopically, on the ultimate prognosis, has been stressed recently by Lahey,[3] who points out that though the five year nonrecurrence rate in carcinoma of the rectum is 37 per cent with lymph node invasion alone, it is only 14 per cent when blood vessel invasion is an added factor.

As illustrated by Willis,[5] the perineural lymphatics constitute an important route of cancer permeation, but without invasion of the nerves themselves. This may account for many of the local and distant bizarre recurrences which are difficult to explain.

It has been demonstrated repeatedly that the size of a rectal malignancy has no bearing upon the presence or absence of metastases; therefore it would be a grave error to consider any case inoperable simply because the rectal lesion was locally extensive.

Anus. The majority of anal carcinomas arise from the anal epidermis and are of a highly malignant epidermoid type. As shown by Gilchrist and David,[6] squamous cell carcinoma of the anus may metastasize to the nodes about the superior hemorrhoidal artery as well as to the more commonly involved inguinal lymph nodes. Therefore, a radical approach is necessary in treating these cases.

DIAGNOSIS

Rectum. Though the diagnosis of rectal carcinoma can be made readily by very simple means, it is still missed with unjustified frequency by many physicians, with dire consequences for the patient. The presence of rectal bleeding, change in bowel habit, or rectal pain should suggest a neoplasm and demand a rectal examination by palpation and proctoscope to rule out the disease. Approximately three-fourths of all malignancies in this area are palpable, and all of them are easily visualized with the proctoscope. It is obvious

that at the present time the greatest advance in this problem can be made by earlier diagnosis of the lesion, and, prefarably, by discovery of rectal polyps and adenomata which can be removed before they undergo malignant degeneration. It follows that to accomplish this, proctoscopic examination must be considered routine for all patients with rectal or anal complaints, and hemorrhoidectomy should not be performed without previous examinations of this type.

Bleeding in rectal carcinoma is the most constant symptom and manifests itself usually as bright red blood either streaking the stool or in larger amounts, mixed with the stool. Massive hemorrhage is uncommon; therefore anemia is usually a late manifestation. Change in the bowel habit may appear as constipation, diarrhea, or alternating constipation and diarrhea, and should be a signal for thorough gastrointestinal investigation. Pain, which most frequently appears as a sense of rectal fullness, is quite variable and usually a late sign, due to the absence of sensory fibers in the rectum itself. It frequently signifies the invasion of surrounding, more sensitive tissue, by the tumor.

Involvement of adjacent organs by direct extension and infection about the primary growth frequently produces symptoms referable to the particular organ involved. The fact that hemorrhoids and anal fistulae are sometimes secondary to rectal carcinoma must constantly be kept in mind.

The appearance of a malignant rectal lesion on proctoscopic examination is so characteristic, with its indurated rolled edges and ulcerated central portion, apparently arising from normal mucosa, that the diagnosis is apparent even to the inexperienced. Biopsy is advisable for confirmation and as a basis upon which to judge the prognosis in the particular case. A negative biopsy calls for a repetition of the procedure.

There is no place for x-ray examination in the diagnosis of carcinoma of the rectum. In fact, it is inadvisable to force barium beyond the lesion for it will frequently complicate the subsequent operative procedure and it may mask the diagnosis. For this reason, it should be a standing rule that a barium enema will not be done in any case until a proctoscopic examination has been completed.

Anus. The diagnosis of carcinoma of the anus rarely presents difficulty because of the relatively superficial location of the lesion. The presence of sensory nerve elements in the anal canal makes pain a prominent feature of this disease and usually brings the patient to medical attention at a comparatively early date. Biopsy will verify the diagnosis.

ANALYSIS OF 100 CONSECUTIVE CASES OF CARCINOMA OF THE RECTUM AND ANUS AT THE ILLINOIS RESEARCH HOSPITAL

In this series of 100 consecutive cases observed at the Illinois Research Hospital during the past few years (1942–1947), it was found that there were 96 cases of rectal malignancy and 4 cases of anal carcinomas. There were 75 males and 25 females in this group. There was only 1 patient in the third decade of life, 2 in the fourth, 12 in the fifth, 33 in the sixth, 33 in the seventh, and 19 in the eighth, with an overall average age of 59.7 years. This is undoubtedly a much older age group than would ordinarily be expected, but is typical of patients seen in a charitable institution. The average duration of symptoms in these individuals, before they came to the hospital for care, was 9.9 months. As shown in Table 1, the most common symptom in this series was rectal bleeding, which occurred in 92 per cent of patients. In 85 per cent there was some type of change in the bowel habit, and 81 per cent complained of pain, or a constant sensation of fullness in the rectum. Loss of weight and weakness were frequent complaints, occurring in 71 per cent and 66 per cent of the patients, respectively. An arbitrary figure of 4,200,000 red blood cells and a hemoglobin of 80 per cent were used to indicate the presence or absence of anemia, and on this basis 41 of the 100 patients were considered anemic when first seen.

TABLE 1

Symptoms in 100 Consecutive Cases of Carcinoma of the Rectum and Anus

(As observed at the Illinois Research and Educational Hospitals)

Symptoms	Percentage of Series with Symptoms	Average Duration of Symptoms (Months)
Constipation	64%	8.10
Diarrhea	56%	7.44
	(85% had constipation or diarrhea)	
Alternating constipation and diarrhea	36%	5.91
Pain (sense of rectal fullness)	81%	7.36
Rectal bleeding	92%	8.29
Total large bowel obstruction (cramps, obstipation, distention, anorexia)	11%	0.25
Loss of weight	71%	7.85
	(average 20.8 pounds)	
Weakness	66%	5.84

Surprisingly enough, none of those patients had undergone a hemorrhoidectomy during the year preceding their admission, although one of the patients was on the operating table in a private hospital preparatory to the procedure, and the grave error was discovered only after an unsuccessful attempt was made to insert a rectal speculum. It is somewhat disturbing to find, however, in reviewing the histories of these patients, that 26 of them received some type of medical care from a physician in the form of suppositories, ointments, oral drugs, etc., for periods ranging from one to nine months, before the patients became discouraged and sought more successful medical aid.

Eleven of the patients had obstruction with symptoms of cramping pain, distention, obstipation and anorexia when they were admitted. The onset of these symptoms is notoriously insidious in these cases and usually the patients are not aware of the seriousness of their disease.

The operability and mortality will be discussed later.

PRE-OPERATIVE TREATMENT

The usual long period of illness in these patients before they come to surgery makes careful pre-operative treatment imperative, if a minimum mortality is expected. They must be restored to a fairly normal nutritional status as rapidly as possible, since the tumor progresses with each passing day. By doing routine examinations, including urinalysis, blood counts, and blood chemistry (particularly blood proteins) as soon after admission to the hospital as possible, the pre-operative treatment will be properly guided. One must not be misled by the normal red count so frequently found because of the dehydrated condition of the patient. The red blood cell count, hemoglobin, hematocrit and blood protein determination should be repeated after dehydration is corrected so that an accurate estimation as to the need of pre-operative blood transfusion can be made. By supplementing a high caloric, nonresidue diet with 1,500 to 2,000 cc. of 5 per cent glucose and 5 per cent amino acids, the patient's dehydration can be corrected, and he will revert to a positive nitrogen balance. The malnutrition present in most of these individuals makes the addition of vitamin B complex and vitamin C to the intravenous fluids necessary for normal postoperative healing. It may be necessary to give as much as 1,500 to 3,000 cc. of blood before the patient may be considered a good operative risk. Although obstruction may be almost complete, vomiting is infrequent because the obstruction is low; therefore hypochloremia is rarely a significant factor. The efficacy of sulfasuxidine or sulfathalidine therapy during the four or five days preceding surgery has been well proved; therefore it should be part of the routine care during that period. For four to five days before operation sulfasuxidine is given in doses equal to 10 to 15 Gm. per day, or sulfathalidine 5 to 6 Gm. per day. There is no danger of toxic manifestations from these drugs as their absorption from the intestinal tract is negligible. On the morning of operation, an indwelling urethral catheter is inserted routinely in both male and female patients.

Although a preliminary colostomy for obstruction may occasionally be necessary in carcinoma of the sigmoid and transverse colon, it is rarely necessary in carcinoma of the rectum because obstruction by lesions in this location is rarely complete.

OPERATIVE METHODS

Rectum. It is beyond the scope of this paper to discuss the numerous operative methods that have been employed to eradicate malignant disease of the rectum, but a few of the more popular procedures will be briefly considered. *There is no one operation* which will be applicable to all cases; therefore it is necessary for the surgeon to become acquainted with various procedures which he may use as the indication arises.

The *abdominoperineal resection,* as described by Miles in 1908, performed as a one stage procedure, is probably the most widely used operation for carcinoma of the rectum at the present time. This procedure entails an abdominal approach first, usually through a left lower paramedian incision, with thorough exploration of the abdomen to determine the extent of the lesion. When it is determined that resection is indicated and technically possible, the peritoneum is freed over the medial, lateral and lower anterior surfaces of the sigmoid colon. Peritoneal flaps are raised and the bladder or uterus is freed from the bowel. The superior hemorrhoidal and in some instances, depending upon the extent of lymph node involvement, the sigmoid artery is then ligated. The rectum is freed by blunt dissection as far distally as the sacrococcygeal junction and the continuity of the bowel is then interrupted well above the site of the lesion. A permanent colostomy is prepared by bringing the proximal loop through either a midrectus or left McBurney type of incision (preferably the latter). The distal loop is ligated or closed with a continuous suture, covered with a rubber glove,

dropped back into the hollow of the sacrum, and the pelvic peritoneum is closed over the distal segment of bowel. The abdominal wound is then closed routinely. The patient is draped for the perineal stage of the operation and after closure of the anus with a purse-string suture, a perianal incision is made. Anteriorly the rectum is dissected free from the prostate gland or the vagina, and posteriorly the rectum is freed from the sacrum by blunt dissection. The distal segment of bowel is removed and the perineal wound is either packed with sponges in a large square of rubber dam or closed about a Penrose drain.

The obvious disadvantage of this procedure is that the patient is left with a permanent colostomy, but it is felt by Lahey,[7] Allen,[8] Jones,[9] Cattell [10, 11] and many others that a radical procedure of this type is an absolute necessity if the greatest number of five-year survivals is to be realized. With proper management of their colostomies, these patients are able to resume their previous routine with very little inconvenience.

The two stage procedure devised by Lahey in 1935 is now being used infrequently, since all surgeons recognize the advantage of the one stage operation. It is being used by him in approximately 15 per cent of his cases at the present time. It is most advantageous in those patients who have an abscess or an inflammatory lesion associated with their carcinoma. In this operation the permanent colostomy is implanted in the left midrectus operative incision and the distal loop is brought out suprapubically. At the second operation the suprapubic colostomy is freed, the rectum prepared for removal through an abdominal incision surrounding the temporary colostomy and the procedure is completed through a perineal incision as in the Miles operation.

Dixon,[12] Wangensteen,[13] Horsley [14] and others have been using an *end-to-end type of anastomosis* by aseptic or open methods in the treatment of rectosigmoid lesions with preservation of the sphincter musculature. These surgeons are of the opinion that segmental resection, as shown by their statistics, is sufficiently safe and radical for lesions of the upper one half of the rectum. Resection in these cases is preceded by the establishment of a temporary colostomy to provide optimum conditions for healing at the anastomotic line.

The procedure of *proctosigmoidectomy,* as devised by Babcock, has been used quite extensively by Bacon [15] with reportedly good results. This operation is also employed as either a one stage or two stage procedure and permits preservation of the sphincter musculature in 80 per cent of the cases. The technic essentially involves an abdominal phase, during which the sigmoid colon and rectum are mobilized, and a perineal phase during which the rectum and a portion of the sigmoid colon are exteriorized and removed. The sigmoid stump is then sutured to the preserved sphincter, either immediately in the one stage procedure, or it is brought out as a perineal colostomy, and the continuity of the bowel with the sphincter is restored at a second operation.

It is apparent from the studies of Gilchrist and David,[6] in which they showed that 60 per cent of all cases of carcinoma of the rectum have local node metastasis, that any operation attempting to eradicate the disease must be radical and remove as much local tissue as possible. The knowledge that spread occurs by veins and perineural lymphatics, as well as through the usual lymphatic channels, makes the radical approach to the problem imperative.

Surgeons are frequently confronted with the problem of whether to do a palliative resection when distant metastases are already present. This certainly is a justified procedure, when the patient is a fairly good operative risk for not only does it prolong his life but it allows him freedom from a miserable existence for his remaining days.

Anus. The highly malignant epidermoid carcinomas are best treated by abdominoperineal resection, as recommended for rectal carcinoma. The recognition that these lesions metastasize to retroperitoneal lymph nodes, as well as to the inguinal nodes makes this operation the logical one. A block dissection of the inguinal lymph nodes is done at a later date (two or three weeks after the radical excision). Very rarely a lesion which is early enough to justify treatment by radon implantation may be found but more frequently this method is reserved for palliation in inoperable cases.

In those patients who cannot withstand the operative trauma of a Miles resection, a *Lockhart-Mummery type of procedure* may possibly be performed. In this operation a sigmoid colostomy is constructed, bringing out both loops of sigmoid, and in a second stage a perineal excision of the rectum with amputation of the bowel at the level of pelvic peritoneum is carried out. In patients who are extremely poor risks this method will result in a lower mortality rate, but the extent of resection is not as radical as in the Miles abdominal-perineal resection.

OPERABILITY, OPERATIVE MORTALITY AND RESULTS

It is extremely difficult to correlate the statistics from various clinics concerning the operability and operative mortality of rectal carcinoma because there are so many different procedures applied to the treat-

TABLE 2

Surgery in 100 Consecutive Cases of Carcinoma of the Rectum and Anus

(As observed at the Illinois Research and Educational Hospital)

SURGICAL TREATMENT	NO. OF CASES	LOCATION OF LESION	TYPE OF OPERATION	COMPLICATIONS	DEATHS	OPERATIVE MORTALITY
Inoperable (no surgery)	10	9 Rectal	None	—	0	0
		1 Anal	None	—	0	0
Inoperable (Colostomy)	21	20 Rectal	Loop colostomy	1 Small bowel obstruction 1 Evisceration 1 Urethral fistula 1 Perforation of proximal loop, peritonitis and death	1	5%
		1 Anal	Loop colostomy	None	0	0
Palliative resection	6	Rectal	Miles resection (one stage)	1 Atelectasis	0	0
Curative procedures	63	61 Rectal	52 Miles resections (one stage)	1 Neurogenic bladder 1 Bilateral femoral vein thrombosis 1 Psychosis—2 wks. 1 Perforation of colostomy 1 Gangrene of sigmoid loop 2 Urethral fistulas 2 Small bowel obstructions 2 Eviscerations 1 Pelvic abscess—peritonitis—death 1 Perforation of colostomy, peritonitis, death	2	3.27%
			3 Lockhart-Mummary (two stage)	None		
			2 Lahey (two stage)	None		
			2 Local resections (end-to-end, two stage)	None		
			1 Posterior excision	None		
			1 Local excision	None		
		2 Anal	1 Miles resection (one stage)	None		
			1 Lockhart-Mummary (two stage)	None	0	0
Total	100	96 Rectal 4 Anal		20.0%	3	3.33%

ment of this disease. Allen [8] in a recent review of 100 cases reported that abdominoperineal resection was possible in 72, seven of which were palliative procedures, and his operative mortality was 28 per cent. In reporting the results of anterior resection for removal of carcinomas of the rectosigmoid, Dixon and Lichtman [16] cite a mortality rate of 5.9 per cent for the entire group of 340 cases, but a mortality of only

1.1 per cent for the 184 resections performed during the past five years. In a follow-up on 272 patients that had been resected, they had a five-year-survival rate of 67.7 per cent. Bacon,[15] reporting on the use of abdominoperineal proctosigmoidectomy, had 80.4 per cent in whom resection was possible and a mortality rate of 6.8 per cent. It has been pointed out by Cattell and Sugurbaker [10] that their percentage of resectable carcinomas of the rectum has increased from 57 per cent in the period 1931–1934 to 85 per cent in 1941. Yet, the total salvage has only increased from 25 per cent to 33 per cent. *They emphasize the disturbing fact that in general the disease is not being diagnosed earlier now than it was ten years ago.* Jones [9] was able to report a series of 550 cases with a mortality of 7.8 per cent and a 52 per cent five-year-survival rate. Lahey,[3] in stressing the need for radical surgery in carcinoma of the rectum, reviewed a large series of his cases and showed 90 per cent five-year-nonrecurrence rate in the patients with no metastases, 37 per cent five-year-nonrecurrence rate in those cases with only nodal invasion, 30 per cent five-year-nonrecurrence rate in those with nodal and adjacent structure invasion and 14 per cent five-year-nonrecurrence rate in those with blood vessel invasion.

Our own resectability rate in 100 consecutive cases of carcinoma of the rectum and anus was 69 per cent, 6 per cent of which was palliative. As shown in Table 2, there were 90 patients operated upon, including 21 with colostomies performed for the relief of obstruction. There were 18 major complications, postoperatively, or an occurrence rate of 20 per cent, and 3 deaths giving an overall operative mortality of 3.33 per cent. However, the mortality rate in the 69 patients upon whom radical resection was performed was only 2.9 per cent, a figure lower than the mortality in colostomy alone. This is explainable by the fact that the patients having colostomy alone were inoperable, many of whom were in a very late stage of the disease. All of the deaths were due to peritonitis, two of them following perforation of the colostomy loop and the third as a result of the rupture of a pelvic abscess.

In general, the five-year-survival rate for carcinoma of the rectum is between 40 and 50 per cent, which is extremely favorable when compared to that in other common malignancies, such as those in the stomach. Since this high survival rate is being attained with the patients reaching surgery in seven to ten months as they are now, it is obvious from results reported in patients without metastases [3] that *the five-year-survival rate would be as high as 85 to 90 per cent if patients could be operated on within two to four weeks after onset of symptoms.*

SUMMARY

One hundred consecutive cases of carcinoma of the rectum and anus, as observed in the Illinois Research and Educational Hospital during the past few years, were studied. The average duration of illness before these patients were first seen was 9.93 months. The most common symptom was rectal bleeding, which was present in 92 per cent of the patients; the next most common symptom was change in bowel habit, observed in 85 per cent of the series. The frequency of resectable cases in the 100 cases was 69 per cent, 6 per cent of which were palliative resections. Twenty per cent of the patients operated upon had some type of major complication postoperatively. However, the mortality rate in the 69 patients having radical resection (both palliative and curative) was 2.9 per cent. One of the 21 cases having colostomy alone died.

The major factors in improvement of pre-operative care during the past few years include protein and blood replacement and the administration of penicillin, streptomycin and sulfathalidine; they have increased the range of operability and lowered the mortality rate. Too much emphasis cannot be placed on the value of proper pre-operative care in maintaining a low operative mortality rate.

It has been pointed out that 75 per cent of all rectal carcinomas are palpable, and all of them are visible proctoscopically. The early diagnosis of these lesions offers the greatest hope for improved survival rates. No patient should be treated for anal or rectal disease, especially hemorrhoids, without proctoscopic examination.

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BOOK REVIEWS

INTERNAL MEDICINE IN GENERAL PRACTICE. By Robert P. McCombs, M.D. Second Edition. 740 pages, 122 illus. Philadelphia, Saunders, 1947. Price $8.00.

This edition is an expanded version of the first edition. New material has been added and the text has been extensively revised.

Dr. McCombs is well fitted to write for the general practitioner. His experience at the Joseph H. Pratt Diagnostic Hospital gives him insight into the physician's problems. In addition he has had the unusual experience of conducting postgraduate work in internal medicine "in the field," as it were, aiding the practitioner in diagnosis and treatment in his office and in the home.

This volume does not replace the ordinary textbook of medicine for it does not go into the detail necessary for the text on the practice of medicine. The author points out that he emphasizes especially those diseases attended by confusion in diagnosis or treatment. To keep the book relatively small Dr. McCombs makes use of valuable tables to present differential diagnosis. Also he uses lists in order to present concisely certain types of information that lend themselves to such *presentation.*

Throughout the book emphasis is placed on the importance of history and physical signs with a description of those simpler laboratory tests which may be of assistance. Well thought out diagrams are used in several instances to clarify the subject matter. The chapter on heart disease is especially good. The various systems are covered in separate chapters. The use of the newer chemotherapeutic agents and antibiotics are well presented in a separate chapter.

As noted above, this book does not replace the more full and extensive textbook of medicine yet the reviewer feels that this is a most valuable book for the general practitioner because of its conciseness and simplified presentation of the physiologic abnormality in disease.

R. H. K.

THE DOCTOR DISCUSSES MORALS. By Winfield Scott Pugh, M.D. 75 pages. New York, William-Frederick Press, 1946. Paper $1.00, cloth $1.50.

The preface to this little book states that the author discusses morals as factual from the viewpoint of a physician, psychologist and anthropologist and not as a moral reformer.

As a medical officer in the U. S. Navy for about two decades Dr. Pugh developed his interest in the sex customs and morals of peoples in many parts of the world. For the past 20 and more years as visiting and consulting urologist to several hospitals in New York City he has interested himself in the moral viewpoints and marital problems of the people of our country.

The author first gives numerous examples to show that morals are a matter of geography and time. Among one people it is as immoral to wear clothing as it is to appear in the nude in this country. A kiss even in the married is considered as immoral in certain parts of the world as it is proper here. Thus Dr. Pugh indicates there is no universal definition of what constitutes morality, it being a matter of custom.

A discussion follows, with examples, of mass hysteria in communities on the subject of sex crimes such as the "gardenia gas" and the "mad anesthetist" of recent years. The Seabury investigations with methods of

(Please turn to Page 81)

Fortunately, most of the vitamins are not harmful, even in large doses. However, two, at least, are and the danger of their use, as well as the uselessness of others under certain conditions are described in this paper.

Fat-Soluble Vitamins
Fallacies of Ill-Advised Therapy*

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PHILADELPHIA, PENNSYLVANIA

Vitamin A and its provitamin, the biologically active carotenoids, vitamins D, K, E and to some extent the essential unsaturated fatty acids such as linoleic and arachidonic acid, constitute the group of fat-soluble vitamins. The fallacies of vitamin medication concern more the choice and lack of proper indications than its possible dangers. In contrast to hormones, the vitamins, although biologically very active, are in general devoid of direct toxicity. Vitamins A and D are the only vitamins which in overdosage may produce specific toxic manifestations.

For vitamin A the toxic dose is far above the usual therapeutic doses. In consequence, it is not surprising that no case of hypervitaminosis A has yet been recorded in clinical literature. In animals overdosage with vitamin A, even with chemically pure crystalline compounds, manifests itself in weight loss, in seborrheic dermatitis, in osteoporosis with multiple fractures and in severe hemorrhagic diathesis. The hemorrhagic tendency is due to a secondary hypoprothrombinemia, based probably on disturbed hepatic function.

Transformation of carotene, as provitamin A, into vitamin A will cease even with excessive doses of carotene—before the toxic range of hypervitaminosis A is reached. Thus, overdosage with carotene will never entail toxic side-effects.

Great and increasing practical significance should be attached to the possibility of clinical hypervitaminosis D. In the case of vitamin D, the large doses currently often used in, and recommended for, various conditions, such as arthritis, lupus, scleroderma and tetany are very close to the toxic limit. In prescribing large doses of vitamin D one should be aware of this danger.

The earliest and most pronounced symptoms of intoxication originate from the digestive system. They manifest themselves by anorexia, nausea, vomiting, abdominal cramps and diarrhea. Polyuria and polydipsia may appear early. Neuralgia, pain in muscles and joints, dizziness, headache, muscular weakness, haziness of memory and, occasionally, numbness and tingling in the extremities may also be included in the list of symptoms. The more severe signs include renal failure, demineralization of long bones and metastatic calcification of soft tissues, including vessels and various organs. The urine in this advanced stage of hypervitaminosis D has a low specific gravity, contains a trace of albumin and many hyalin and granular casts. Serum calcium is usually elevated, but may be found to be within normal limits even in a severe toxic condition. An increase of nonprotein nitrogen and creatinine in the serum accompanies far advanced renal failure.

The syndrome of hypervitaminosis D is identical with the toxic condition observed after overdosage with parathyroid hormone, and also after overdosage with the toxic irradiation product of ergosterol, called di-hydrotachysterol or A.T. 10. This latter compound has been used in daily doses of 5 to 10 mg. for the treatment of parathyroid tetany.

In small doses vitamin D has a marked influence on the resorption of calcium from the intestinal canal. In contrast, parathyroid hormone and di-hydrotachysterol, as well as excessively large doses of vitamin D, mobilize the calcium from the bones and the resorption-increasing effect is not demonstrable.

Admittedly, various forms of vitamin D differ in their toxicity. There is, however, no vitamin D preparation which would be devoid of toxicity when given in large doses. In the recommended doses of 200,000 units of vitamin D daily, given for a prolonged period, toxic manifestations are a relatively common occurrence. The potential toxicity of large doses of vita-

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Paper given as part of a Symposium on "Vitamins and Hormones" at the 11th Annual Postgraduate Institute of the Philadelphia County Medical Society, April 15, 1947.

min D is enhanced by a diet rich in calcium, such as the predominantly milk diet of infants. Patients show great variation with regard to their inherent resistance to the toxic effect of large doses of vitamin D.

Reports on severe and even fatal toxic manifestations following vitamin D therapy are appearing in progressively increasing numbers in the literature of the last few years. The question arises whether or not this possible danger is justified by the possible benefit. An analysis of the situation in various conditions is given below.

Arthritis. *A critical review of the literature supports the statement of the American Rheumatism Association in 1942 and of various authors, that large doses of vitamin D are of doubtful value in the treatment of arthritis and do not seem to alter the ultimate course of the arthritic process. Thus, in the absence of well-founded therapeutic indications, a warning against the use of massive doses of vitamin D over a prolonged period of time in arthritis should deserve serious consideration.*

Parathyroprival Tetany. *The treatment of this condition with massive doses of di-hydrotachysterol (5–10 mg. daily) or—preferably—of vitamin D (200,000 units daily) is based on a solid scientific foundation. As a matter of fact there is practically no therapeutic alternative to the use of the compounds named. In consequence, the treatment with massive doses of vitamin D (or di-hydrotachysterol) may be recommended, provided the adjustment in the patient's condition is strictly supervised, with special reference to possible clinical and chemical manifestations of threatening hypervitaminosis D.*

Scleroderma, Lupus, Tuberculous Empyema. *Recently massive doses of vitamin D, 50,000 to 150,000 units daily, have been advocated for the treatment of lupus, scleroderma, tuberculous empyema and other tuberculous conditions. Favorable results were claimed. For instance, in a group of 32 cases of lupus vulgaris, 18 appeared to be cured of the disease; in nine, well marked improvement has taken place; in five, improvement has been only moderate. More well-controlled observations are needed in order to weigh properly the advantage of therapeutic achievement over possible dangers of overdosage.*

Under normal dietary conditions vitamin D has to be supplied as a separate supplement only in normal therapeutic or prophylactic doses, 400 to 800 units daily (or produced by direct irradiation), for infants, children and pregnant women. The requirement for the rest of the fat-soluble vitamins is, as a rule, well covered by the diet, and for vitamin K, by intestinal synthesis.

Crude cod liver oil of relatively low vitamin A and D potency is not a satisfactory vehicle for vitamins A and D. In infants receiving the usual relatively large prophylactic or therapeutic doses of medicinal cod liver oil, electrocardiographic changes and other toxic manifestations were described by Agduhr as early as the late 20's. In animals (pigs, rats) incorporation of crude cod liver oil in the diet may lead to fatal liver necrosis. This "toxic" effect of crude cod liver oil is due mainly to the presence of unnatural unsaturated fatty acids which in turn may destroy, through peroxide formation, vitamin E and perhaps other essential substances in organs and tissues. Thus, in the practice of vitamin A and D medication it would appear to be advisable to substitute high potency fish oils (halibut, shark), fish oil concentrates or distillates as well as vitamins D_2 or D_3, produced by irradiation, and carotene for the medicinal crude cod liver oil of low potency. These substitutions will permit elimination of fish oil altogether or a considerable reduction of its intake.

Among fallacies of therapy with vitamin A the error of the claim for its anti-infective effect is now generally recognized. It may also be stated that the assumption of widespread vitamin A deficiency among the population is almost certainly false. It was based on the misinterpretation of biomicroscopical findings of conjunctival changes and on unsatisfactory dark-adaptation tests. Large doses of vitamin A (150,000–200,000 units) daily were recommended for various skin diseases such as Darier's disease, also for vaginal leukoplakia. There are not enough well-controlled observations available to form a final opinion as to the efficacy of the treatment.

Reduction of blood pressure in hypertensive patients or animals has been attributed to fish oils as source of vitamin A, when given by mouth over a sufficient period of time. Further studies have definitely established the independence of this alleged antipressor effect from vitamin A. It has been surmised that the antipressor effect of fish-oils may be due to some unidentified oxidation product of vitamin A or of some other constituent of fish oils. The antipressor effect was demonstrable in only a few fish-oil samples and there are no means available as yet for its exact detection. Owing to its erratic nature the observation has not attained any practical significance. The same reservation applies also with regard to a similar claim concerning vitamin K-like compounds.

In case of idiosyncrasy to fish, carotene, which is always of vegetable origin, may be substituted for vitamin A concentrates obtained from fish oils.

The source and vehicle of fat-soluble vitamins are fats. Disturbance of fat digestion will lead to impaired absorption and utilization of fat-soluble vitamins. The classic example is vitamin K deficiency following obstructive jaundice. It is obvious that in patients suffering from obstructive jaundice, vitamin K should be given parenterally, by intramuscular injection. Only the water-soluble modifications of vitamin K—and there are several such preparations on the market—may be used by mouth when fat-absorption is markedly reduced. As for many other vitamins, there is a tendency to use too large doses of vitamin K when smaller doses would assure the same satisfactory result. Daily, 5 to 10 mg. should suffice in the most severe cases of vitamin K deficiency.

A common fallacy of vitamin K therapy is the reliance on the medication itself. The hemorrhagic diathesis characteristic of vitamin K deficiency is based on a low prothrombin level in the blood. In the presence of profoundly disturbed liver function, vitamin K may not be utilized for prothrombin production and hypoprothrombinemia may persist in spite of prolonged vitamin K medication. In consequence, before any major surgical interference in patients with obstructive jaundice it is imperative to check the prothrombin time as such, regardless of previous adequate vitamin K medication.

Massive salicylate therapy may depress the prothrombin content of the blood. A combination of salicylates (including aspirin) with vitamin K is indicated when given in large doses, as in rheumatic fever.

The role of vitamin E (tocopherol) in the clinic as well as in normal nutrition is in many respects still obscure and requires further elucidation. The claims for its therapeutic effect in various diseases, as in progressive muscular dystrophy and amyotrophic lateral sclerosis, have either been definitely refuted or remained so far unconfirmed, as in habitual abortion, myocarditis and Dupuytren's contracture. On the other hand, more and more experimental data have been amassed during the last few years to show the importance of vitamin E (tocopherol) as a powerful biological antioxidant. As such it protects not only easily oxidizable fatty or fat-soluble substances (including for instance vitamin A, carotene and unsaturated fatty acids) in the test tube and apparently in the living organism—in the intestinal tract and beyond it, in the living tissues.

Little is known about the requirements of man for unsaturated fatty acids. It has been repeatedly stated, that the specific role of the essential fatty acids in man, particularly in infants and young children, is that of restoring and maintaining normal nutrition of the skin. Essential fatty acids have been recommended as a valuable adjunct for the treatment of infantile eczema. It may be expected that future studies will shed light on the important interrelation between essential fatty acids and vitamin E. Only then will we be able to establish the normal figures for human requirement of essential fatty acids as well as of vitamin E, and assess their role under various pathologic conditions.

BOOK REVIEWS (Continued from Page 78)

"framing" girls are described. Space is given to examples of pathologic lying, and false accusations by women and girls of men alleged to have attacked them. The psychiatric implications are portrayed.

From the anthropologic viewpoint the author points out that among primitive people, where knowledge relative to all things sexual is universal from childhood on, sex crimes (rape and murder of women and girls) do not take place. His thesis is that "sexual forces insist on having an outlet and will do so, law or no law." He feels that the banning of prostitution by the reform elements is the cause of an increased number of sex crimes because of the law of nature.

Just as respiration cannot be stopped, nor urinary secretion controlled so Dr. Pugh says the production of spermatozoa goes on. As the distended bladder creates the desire and need for its emptying so the accumulation of spermatozoa distending the seminal vesicles creates sexual urge and need for evaculation. The author admits that some men may remain continent but he says the majority cannot or will not. He more or less argues for recognized prostitution, for he says, "If we would avoid sexual crimes, there must be some substitute for prostitution. What substitute do we offer? The answer is still unpleasant for it is somebody's daughter."

R. H. K.

DISEASES OF THE CHEST; With Emphasis on X-ray Diagnosis. By Eli H. Rubin, M.D. 685 pages, 355 illus. Philadelphia, Saunders, 1947. $12.00.

This new book is an excellent condensation of a vast amount of practical material on diseases of the

(Please turn to Page 84)

The author presents the use of estrogens for menopausal symptoms from a sane and rational viewpoint.

A Critical Survey of the Use of the Estrogens in the Treatment of the Menopausal Syndrome

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The widespread use of the estrogenic and estrogenic-like substances has led to their indiscriminate use in many instances. Their limitations, injudicious use and potential dangers should be emphasized.

The estrogens have their greatest use in the treatment of the menopausal syndrome. It has been estimated that only about 10 per cent of patients having symptoms during the menopause require treatment with the estrogens.[1] It is customary at the present time to use this drug almost routinely for anyone during this period. The effectiveness of the estrogens for the treatment of the menopausal syndrome is difficult to evaluate. Psychotherapy, placebos and sedation are as effective in the greater number of cases. The estrogens have been used for a wide variety of conditions other than the vasomotor instability during the menopause. Conflicting results have been reported for the treatment of leukoplakia, puritis vulvae, arthritic pains, hypertension, edema, intestinal pains, hyperglycemia, respiratory and circulatory disturbance, dysuria and incontinence and involutional melancholia. When one considers the cessation of menstruation and the transition of the individual from the child-bearing period to one in which nature withdraws this function to protect her from the strain of pregnancy and childbirth, one can realize that this is an integral part of the process of aging and in no sense should it be regarded as a disease. Ovarian involution and the consequent estrogen withdrawal is only one of the many changes incident to the aging process and it is difficult to believe how mere replacement therapy can greatly alter or control this complex symptomatology.

THE SOURCE AND POTENCY OF THE ESTROGENS

A clear understanding of the source, derivation and activity of the estrogenic substances is essential to their proper administration. The estrogenic hormone is one of the two ovarian hormones. Although the original source of this substance is the follicle of the ovary, a number of metabolically changed substances are available from other sources, such as blood and urine. All of these active principles obtained from natural sources have been termed the natural estrogens. Their clinical source is derived chiefly from the urine of pregnant women and pregnant mares. The commercial products on the market today vary in potency and there is confusion as to the methods of standardization. Estradiol is generally conceded to be the true follicular hormone found in the ovary. Estrone, or theelin, estriol or theelol are excretion products of estradiol. The potency of the more commonly used estrogens per unit weight is in the following order, beginning with the least potent: (1) Estriol, a product used orally and designated commercially as Theelol (Parke, Davis), Emmenin liquid or tablets (Ayerst-McKenna), Folestrin granules (Armour) and Amniotin capsules (Squibb); (2) Estrone (Lilly), Estrone (Abbott) and Amniotin (Squibb); (3) Estradiol benzoate, also an intramuscular product, as Progynon-B (Schering); Ben-ovocylin (Ciba) and Dimenformon (Roche-Organon); (4) Estradiol dipropionate, Progynon DP. (Schering), and Di-Ovocylin (Ciba), the last two products having the most prolonged effect. The estrone products are derived from urine and estradiol products obtained by the hydrogenation of estrone.

Estrone and its derivatives are usually assayed in international units while the estradiol preparations are assayed in rat units. The rat unit is three to five times as potent as the international unit. One international unit of estrone has a specific estrus-producing activity of 1/10,000 mg. of the crystalline estrone standard, hence 1 mg. of estrone equals 10,000 international units.

In addition to the natural estrogens, certain synthetic products have been derived which, although not chemically related to the natural estrogens, have similar physiologic action. The more common ones are stilbestrol, Octofollin and hexestrol. Stilbestrol has an estrogenic potency three to four times that of estrone. Its side effects, such as dizziness and nausea, detract

from its efficiency. Hexestrol is a less potent and less toxic preparation. Octofollin, another synthetic preparation, is similar in its action and toxicity to hexestrol. The chief advantage of the synthetic estrogens lies in their low cost and their effectiveness when given orally.

Recently two oral estrogens have received considerable publicity, their advantage being that they are natural estrogens, effective orally, with relatively few side effects. These are Premarin (Ayerst, McKenna) and Estinyl (Schering). Premarin is a conjugated form of the natural estrogens and Estinyl or ethinyl estradiol, a derivative of estradiol. These were first developed by Inhoffen and Hohlweg.[2] It has been reported that this estrogen is 26 times as potent as hexestrol, and 7.5 times at potent as diethylstilbestrol.[3]

THE PHYSIOLOGIC ACTIONS OF THE ESTROGENIC HORMONES

The following are the principal physiologic actions attributed to the estrogens.

1. The relief of menopausal symptoms. With the normal aging of the ovary it becomes refractive to stimulation from the gonadotropic principle of the pituitary. The ovary first fails to ovulate, which is the first break in the endocrine cycle. Failure of ovulation is followed by the absence of the corpus luteum with its progestational influence. This may occur months before menstruation ceases and anovulatory bleeding begins. During this phase the ovary fails to respond to the luteinizing gonadotropic hormone (prolan B), it may still continue to be stimulated by the follicle-stimulating hormone and an excess of estrogen be produced. During this phase abnormal bleeding is apt to occur.[4] With this cessation of the ovarian hormone production an increase in the gonadotropic principle from the pituitary becomes evident in the urine. Whether this is due to an increase in the production of the gonadotropic principle of the pituitary or failure of the ovary to utilize it is uncertain. This increase in the gonadotropic hormone from the pituitary, however, gives rise to many of the menopausal symptoms, and also affects the other glands of internal secretion. Thyroid disturbances are noted, diabetic conditions may become noticeable, and increased growth of hair from adrenal stimulation is also sometimes seen. Nervous instability and tension frequently develop at this time. The vasomotor symptoms arising from the increase in the gonadotropic principle is partly responsible; however, other factors may add to this nervous reaction. The fear of aging, malignancy, economic insecurity and being less attractive to their husbands are all factors in the production of this mental instability.

2. Estrogens promote vascularization of the uterus and with cessation, there is an atrophy of the uterus, genitalia, breasts and skin.

3. Excessive production or administration of the estrogens leads to a hyperplasia of the endometrium. Fibroids have been produced experimentally in animals.[5] Its carcinogenic potentialities have been considered serious by many authorities.[6] Through constant stimulation to the endometrium over long periods of time, changes varying from hyperplasia to a definite neoplastic growth are produced.

4. Withdrawal of the follicular hormone is thought to be one of the factors in inducing menstruation.

5. Contractions of the uterus are stimulated by the estrogens and the uterine muscle is sensitized to the action of pituitrin.

6. It suppresses lactation by its inhibitory action on the anterior lobe of the pituitary.[7]

7. Other changes have been attributed to this substance such as increasing the tone of the vesical muscle, producing hyperemia of the nasal mucosa, increasing libido and many others.[7]

THE USE OF THE ESTROGENIC HORMONE IN THE TREATMENT OF THE MENOPAUSAL SYNDROME

It has been previously stated that only about 10 per cent of patients undergoing the menopause should be treated with the estrogens. Their effectiveness is limited and the potential dangers from the prolonged administration do not justify their use except in the cases uncontrolled by psychotherapy and sedation. The first step in the treatment of the menopausal syndrome is to assure the patient that she is going through a normal process, that she does not have cancer, that the excessive and injudicious use of "shots" or "injections" will only prolong the termination of her unpleasant symptoms and that with the cessation of menstruation she may be relieved of many of the distressing symptoms associated with the menses: fear of becoming pregnant, menstrual cramps and the general unpleasantness of menstruation. This form of psychotherapy along with mild sedation is sufficient in most cases. However, in a few cases, because of the severity of the symptoms, the estrogens are indicated. These should be given in such a manner that they can be terminated within a few months. Oral therapy should be tried first, giving stilbestrol 0.25 to 1 mg. daily at bedtime for a period of 20 days, followed by a rest of seven days. The dose should be kept at a minimum, explaining the reason so that at the end of

several months the medication can be discontinued. Estrone sulfate may be administered in a similar manner if toxic symptoms arise from the use of stilbestrol. During this period an important supplement to this treatment is the improvement of the general physical condition through vitamin therapy, the correction of any anemia, hypothyroidism, or other abnormalities that may exist.

The parenteral administration will be required in a relatively few cases. It should be administered in doses of 10,000 to 20,000 I.U. every four days for three to six doses, gradually increasing the interval so that the medication can be discontinued within six months. Many cases have had the medication continued for years with no program of withdrawal, or no explanation given to the patient for discontinuing the therapy.

CONTRAINDICATIONS TO ESTROGENIC THERAPY

Estrogenic therapy should never be used in the presence of carcinoma or following the treatment of any malignant disease. With irregular and increased bleeding which is so frequent during this period the estrogens should not be used; many instances have been reported where the bleeding stimulated by the estrogens has masked the development of cancer. A diagnostic curettage is always indicated if the bleeding does not cease after the estrogenic substance has been discontinued. However, many curettments are done needlessly because of the stimulation produced by the estrogens. The medication should never be used continuously, but rest periods should be interspersed every three or four weeks. Estrogens should not be given after radiation or x-ray has been used to control bleeding. I believe that the continued use of the estrogens over a long period of time produces severe mental trauma by prolonging the termination of the menopausal syndrome and keeping the patient in a continued state of mental unrest.

Their carcinogenic properties have repeatedly been emphasized, the production of endometrial hyperplasia of all degrees, the association between granulosa cell tumors and endometrial carcinoma and the experimental development of tumors in animals all indicate the potential dangers of this hormone.

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BOOK REVIEWS (Continued from Page 81)

chest. The essentials of applied anatomy, physiology and pathology are presented in a manner which encourages proper evaluation of symptoms, signs, roentgen films and various therapeutic procedures. In emphasizing x-ray in the detection, diagnosis, and prognosis of chest disorders it brings to the general practitioner a means of understanding the methods used by roentgenologists in chest diagnosis. The main part of the book is devoted to specific acute and chronic infections, bronchial diseases and obstructions and affections of the mediastinum, pleura and diaphragms. The characteristic and more probable courses of each disorder are highlighted by well chosen case summaries. Controversial subjects are handled without dogmatism so that the reader senses the majority opinion of the day and certainly is not left to choose sides between conflicting theories. The section on surgical procedures, like the main body of illustrations of x-ray, is not intended to make a specialist out of the reader. However, both make for better understanding of the assistance that these specialties have to offer the general practitioner. The illustrations are numerous and of excellent quality. While this book is primarily intended for the general practitioner, it can be strongly recommended to medical students. Internists, surgeons, and radiologists will find its style appealing and of definite help in brushing up for staff conferences, teaching rounds or lectures.

The author, Dr. Eli H. Rubin, and his surgical collaborator Dr. Morris Rubin are well qualified to present this book because of their appreciation of the fundamentals of chest diseases, their considerable experience on the chest services of Montefiore Hospital, Country Sanatorium, Triboro and Morrisania City Hospitals of New York City and Dr. Rubin's experience as Chief of Thoracic Surgery for the 69th General Hospital Unit.

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From a large number of cases studied the authors present the clinical picture of atypical pneumonia. Its clinical course is described and the effects of treatment evalued.

Primary Atypical Pneumonia: The Diagnosis and Treatment of 440 Consecutive Cases without a Fatality

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In the armed forces, it appears that primary atypical pneumonia occurs more commonly than all other forms of pneumonia combined. It occurs even more commonly than is suspected in civilian life as well. Yet because the disease varies so widely in its clinical manifestations it may be difficult to establish a trustworthy diagnosis in many cases. The present study is based on an analysis of 440 consecutive cases of primary atypical pneumonia with no fatalities which occurred during the period of June 1943 to June 1946. Since the symptoms are not characteristic and the signs are frequently nebulous, the diagnosis in each case was corroborated by serial x-ray studies and other laboratory aids. Much of the present literature on the subject is contradictory and it is hoped that this study will contribute to the clarification of some phases of the disease, especially in respect to diagnosis and treatment.

ETIOLOGIC FACTORS

Practically every patient had been examined on several occasions previously and found to be in good health. Most of the cases occurred during the first eight weeks of military service, the period of greatest physical and mental readjustments. Factors involved were increased exposure to the elements, overexertion, psychosomatic factors such as tension and worry, interference with sleep due to change of hours and various duty details, and readjustment of body habits resulting in states such as constipation. Of considerable importance was the influence of droplet infection due to sleeping, messing and class attendance in close proximity to others. Seasonal variations and climate appeared to have little influence as shown by the study over a three-year period.

The work of some investigators [1] suggests that one primary incitant may be a virus. It is not completely established that this is the sole cause. There appear to be reasons for thinking that primary atypical pneumonia may be caused by the synergistic effects of both a virus and a bacterium.[14]

Age. The age of the patients ranged from one to 50 years with an average age of 23.6 years. This is in agreement with the high incidence in young adults found in civilian practice by Smith.[2] Age is a most important factor in low mortality rates since resistance to the pneumonias is highest in young adults.

Sex and Color.

SEX	WHITE	BLACK	INDIAN
Male	419	12	1
Female	8	0	0
Totals	427	12	1

The greatest preponderance of the cases occurred in white males. Although a considerable number of American Indians passed through the post, only one developed the disease in three years. This may be of interest since this race is susceptible to other pulmonary infections such as tuberculosis. The black race was also considerably less susceptible than the white. (No accurate conclusions can be drawn because exact figures for racial distribution of troops were unavailable.)

Prodromal Stage. There is disagreement in the literature concerning the occurrence of prodromes. Some report no prodrome while others stress an antecedent cold.[4] It is our observation that this occurs in almost every case. The shortest prodromal stage was 15 hours, the longest 14 days. The average period was four days. It usually consisted of chilly sensations, slight fever, anorexia, nausea and malaise. Sore throat, headache and generalized aches also occurred. It was much less severe but longer in the primary atypical group than in a comparative pneu-

We are indebted to Lt. I. Goldberg and Lt. M. Yettra for assistance in compiling the charts and statistics.

mococcic pneumonia series. Hence, the former did not seek hospitalization till much later in the disease.

SYMPTOMS

The more important symptoms are listed:

Symptoms	Cases	Per Cent
Malaise (weakness, fatigue, aches)	368	83.6
Cough	340	77.3
Sputum	103	23.4
Chest pain	94	21.4
Chills	55	12.5
Sore throat	30	6.8
Headache	24	5.5

Cough was present in 340 cases (77.3 per cent). It frequently persisted after resolution was completed. *It was nonproductive in most cases for the first 7 to* 12 days. Sputum was absent on admission in 337 cases (76.6 per cent), slight 83 times (18.9 per cent) and profuse 20 times (4.5 per cent). Of these the *character of the sputum was mucopurulent* 84 times (81.6 per cent), bloody 13 (12.6 per cent) and rusty 6 (5.8 per cent). The degree of dyspnea depended on the amount of pulmonary involvement, anemia, toxemia and complications. *Cyanosis was difficult to evaluate* accurately but usually corresponded to the degree of dyspnea.

Physical Findings

Temperature ranged from 98.6° F. to a maximum elevation of 104° F. The average temperature peak for the entire series was 100.2° F. As was to be expected, most cases of primary atypical pneumonia were admitted with normal temperatures compared to pneumonias due to specific organisms which had a more explosive onset. The fever of the former almost always fell by lysis.

Pulse ranged from 78 beats per minute to a maximum of 142. The average rate was 94. As a rule the pulse rate was comparatively slow in relation to the temperature.

Respirations ranged from 16 per minute to 45 with *an average rate of 23.*

Physical Signs. Much emphasis has been laid on the absence or scarcity of physical signs as an important point in differentiating pneumococcal pneumonias from primary atypical pneumonia.[2, 5] Our findings are in agreement.

Pulmonary Physical Findings on Admission:

Positive signs	274	*62.3 per cent*
Signs absent	166	37.7 per cent

The most persistently positive finding was râles in 317 cases (72.0 per cent). They occurred at a later stage of the disease, usually several days after the onset and accounted for many initial erroneous impressions. Dullness of varying degree was elicited in 54 cases (12.3 per cent) while only 30 (6.8 per cent) showed frank tubular breathing. There was a distinct lag in the appearance of clinical findings in the primary atypical form compared with the x-ray changes noted at the same time. The type of râle that is usually heard is medium moist to wheezing in nature, becoming coarser during resolution, compared to the râles of the pneumococcic form of pneumonia which are crepitant and subcrepitant in character. Pectoriloquy was seldom elicited unless there was massive involvement, but suppressed breath and voice sounds were quite common.

Involvement of Other Organs.

Severe tonsillar involvement	8 cases
Enlarged spleen	1
Enlarged liver	1
Marked lower right quadrant tenderness	1

The enlarged spleen was probably due to acute toxic splenitis since malaria and other causes for splenomegaly were ruled out. Marked cloudy swelling may have been the cause of hepatomegaly in one case. Marked lower right quadrant pain was probably reflex from the pulmonary involvement.

Involvement of Lobes. Basal involvement of the lungs was found on x-ray in the great majority of the cases (85.5 per cent). This figure approximates that of others.[6] It is claimed that the frequent ambulatory state of the patient may be responsible.[7] The lobes were involved as follows:

Lobes	Cases	Per Cent
Right lower	165	37.5
Left lower	148	33.6
Right middle	29	6.6
Right upper	21	4.8
Left upper	14	3.2
Two or more	63	14.3

The figures show that the right chest as a whole is involved to a greater extent than the left side (Fig. 1). The more vertical angle of the right main bronchus and relatively decreased mobility of the *right diaphragm* may be factors in the more frequent involvement of the right lung. Scadding [8] classifies the lesions in primary atypical pneumonia as either benign circumscribed pneumonia or disseminated focal pneumonia. The former is not sharply defined but fairly well localized, has uniform density and usually in-

volves the lower lobes. The latter consists of diffuse coarse mottlings with foci varying from 2 to 5 mm. in diameter. Even when an entire lobe appeared involved on posterior-anterior views, the lateral projection revealed incomplete lobar involvement with a confluent bronchopneumonia.[9] The extent of the lesion by roentgenogram is almost always greater than that anticipated by physical examination. This is in agreement with roentgenographic studies by others.[6]

There remains at present some question as to the exact pathogenic nature of the pulmonary lesion of atypical primary pneumonia.[10] It is essentially an acute inflammation of the wall and surrounding tissues of the bronchi and bronchioles. There is a predominant infiltration of round cells and lymphocytes with marked edema giving rise to atelectatic areas.

Admission Diagnoses

It is understandable, perhaps, that the nebulous character of the lung findings leads to such a large percentage of false pre-admission diagnoses (58.9 per cent) when one considers the delayed appearance of typical findings in the majority of the cases. The correct diagnosis was subsequently established by following the clinical course, serial x-ray studies and other laboratory aids. The most important of these was the roentgenogram. The pre-admission diagnoses in 259 cases (58.9 per cent) falsely diagnosed were distributed as follows:

Nasopharyngitis	122 cases
Bronchitis	93
Upper respiratory infection	24
Influenza	13
Pleurisy	4
Malaria	2
Heat exhaustion	1

Laboratory Aids

Blood Studies. Comparative studies with 17 cases of pneumococcic pneumonia revealed the total white and differential counts as shown in Table 1.

The white cell count is usually considered an important differential diagnostic aid. We cannot subscribe to the usual emphasis laid upon such studies since the white count in atypical forms may rise considerably. Even the difference between the mean

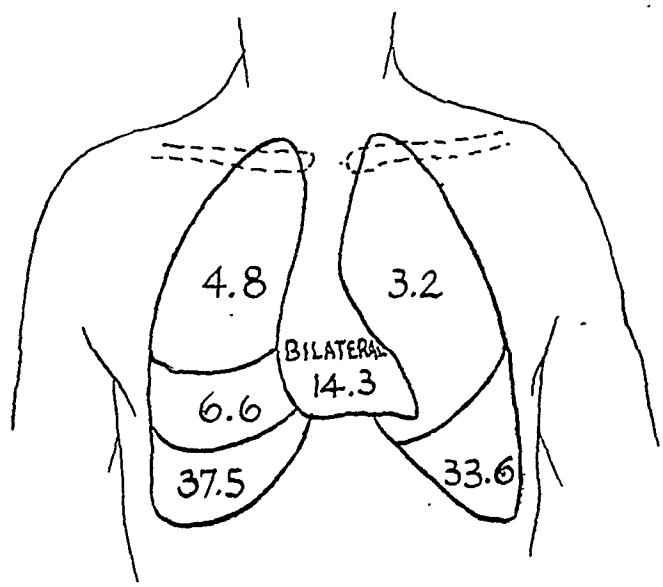


Fig. 1. Diagram of percentage involvement of lobes.

counts is not great enough to place too much reliance on the white cell count in every case. Factors which frequently change the expected response are: complications arising from the primary atypical form, variable virulence of both virus and pneumococcic forms, sulfonamide effect on the presence of secondary invaders and the resistance of the host. The differential counts were inconclusive on numerous occasions making this laboratory study assume less significance. Of course, the presence of a very marked neutrophilia practically never occurs in the atypical form unless a secondary complication develops. The white cell count averaged 11,440 in primary atypical pneumonia and 15,600 in the pneumococcic form. When a marked elevation of the polymorphonuclear neutrophiles occurs it was usually in favor of the bacterial pneumonias.

Urine. The following positive urinary findings occurred in the series:

Albumin	14 cases
Red blood cells	9
White blood cells	6
Casts	2
Sulfa crystals	4

Albumin was present in one to two plus amounts in 14 cases, only one of which was associated with

Table 1

	White Count			Polymorphonuclears (per cent)			Lymphocytes (per cent)		
Type	High	Low	Av.	High	Low	Av.	High	Low	Av.
Atypical	34,000	4,600	11,440	93	44	67	56	7	24
Pneumococcic	25,600	5,600	15,600	93	62	78	38	7	24

nephritis. The others were probably due to cloudy swelling of the kidneys. Sulfonamide reactions accounted for the appearance of red cells in eight cases. Subacute glomerulonephritis resulted in hematuria in one case while eight others were due to mild sulfonamide reactions. Unclumped white cells occurred in six cases, never appearing in quantities of more than five to ten cells per high power field. They were not considered as due to a suppurative involvement of the urinary tract. Casts (never more than one to two per high power field) were found twice. Sulfonamide crystals were present in sufficient numbers to be seen in four cases on microscopic urinary examination.

Sputum. The character of the sputum has been tabulated under symptoms.

Acid-fast stains were indicated in 37 cases for differential diagnosis. Although one to five tests were done in each case no tubercle bacilli were found. Sputum examinations also revealed 15 positive smears for organisms resembling streptococci. No special significance applied since they were either normal inhabitants of the upper respiratory passages or secondary invaders.

Serology. Ten patients had positive serologic tests for syphilis. Of these, one actually developed an initial chancre one week after hospitalization. Two patients were receiving antiluetic therapy. The remaining seven cases (1.5 per cent) were considered false reactions since the Kahn titers were very low and rechecks were negative.

Blood Cultures. Indications for blood cultures were high fever, signs of septicemia, finding of pneumococci in sputum or the presence of complications. No evidence of blood stream invasion was found in 25 cultures performed in the most seriously ill cases.

Sedimentation Rates. The modified Cutter method was performed within the first three days of admission. Studies were repeated at intervals as an aid in determining the progress of infection. About a tenth of all cases showed a normal sedimentation rate at the time the roentgenogram showed signs of pulmonary involvement. The peak elevations of the rates were analyzed and it was found that they ranged from six mm. per hour to a maximum rise of 100 mm. with an average peak of 25 mm. Frequently there was no abnormality in the sedimentation rate when pneumonic involvement was minimal. On the other hand, it occasionally remained slightly elevated for varying periods after the lungs showed complete clearing by roentgenogram.

Miscellaneous Studies. Certain conditions may resemble primary atypical pneumonia necessitating appropriate laboratory procedures for differentiation. These include brucellosis, rickettsial diseases (typhus and Q fevers), bacterial pneumonias (tularemia, streptococcus, etc.), pulmonary tuberculosis, coccidioidomycosis, ornithosis, influenza A and B, lymphocytic choriomeningitis pneumonia and malaria. Although there was no history of having entered an endemic area, because of slow resolution of hilar involvement a coccidiodin skin test was performed on one occasion and was negative. Four malaria smears were negative. Agglutination tests for brucellosis, tularemia and typhus fever were performed once each and found negative. Since serologic tests, such as cold-hemagglutination and streptococcus MG agglutination, do not give positive results in about half the cases, they were not employed routinely. The former is positive in only 56.7 per cent of the cases [11] while the latter is positive in only 48.9 per cent.[12] There are numerous false positive reactions in unassociated diseases.

PRE-EXISTING DISEASES

In 17 patients, pneumonia developed during the course or convalescent period of the following conditions: otitis media, 5 cases; syphilis, 2 latent and 1 primary; and one case each of chronic ethmoid sinusitis, infectious hepatitis, measles, arrested pulmonary tuberculosis, moderate bronchiectasis and subacute glomerulonephritis. The last condition was probably reactivated by the pneumonic involvement. Whether bronchiectasis resulted in acute peribronchiectatic pneumonitis or was a true case of primary atypical pneumonia was difficult to determine in one case. The course and findings were more suggestive of the latter.

COMPLICATIONS

Secondary complications or other diseases following the onset of pneumonia were present in 20 cases (4.5 per cent). They are listed as follows:

Serofibrinous pleurisy, acute	5 cases
Otitis media, acute	5
Empyema	1
Myocarditis, acute infectious	2
Measles	2
Thrombophlebitis with pulmonary embolism	1
Varicella	1
Impetigo contagiosa	1
Skin allergy (penicillin)	1
Secondary anemia, severe	1

Both cases of measles developed after the onset of primary atypical pneumonia and are not to be confused with another case of pre-existing measles. One patient, 18 years of age from a rural district, showed a remarkable tendency to successive virus infections, developing atypical pneumonia, measles and varicella in rapid succession shortly after entering the army. None of the otitis media cases required myringotomy.

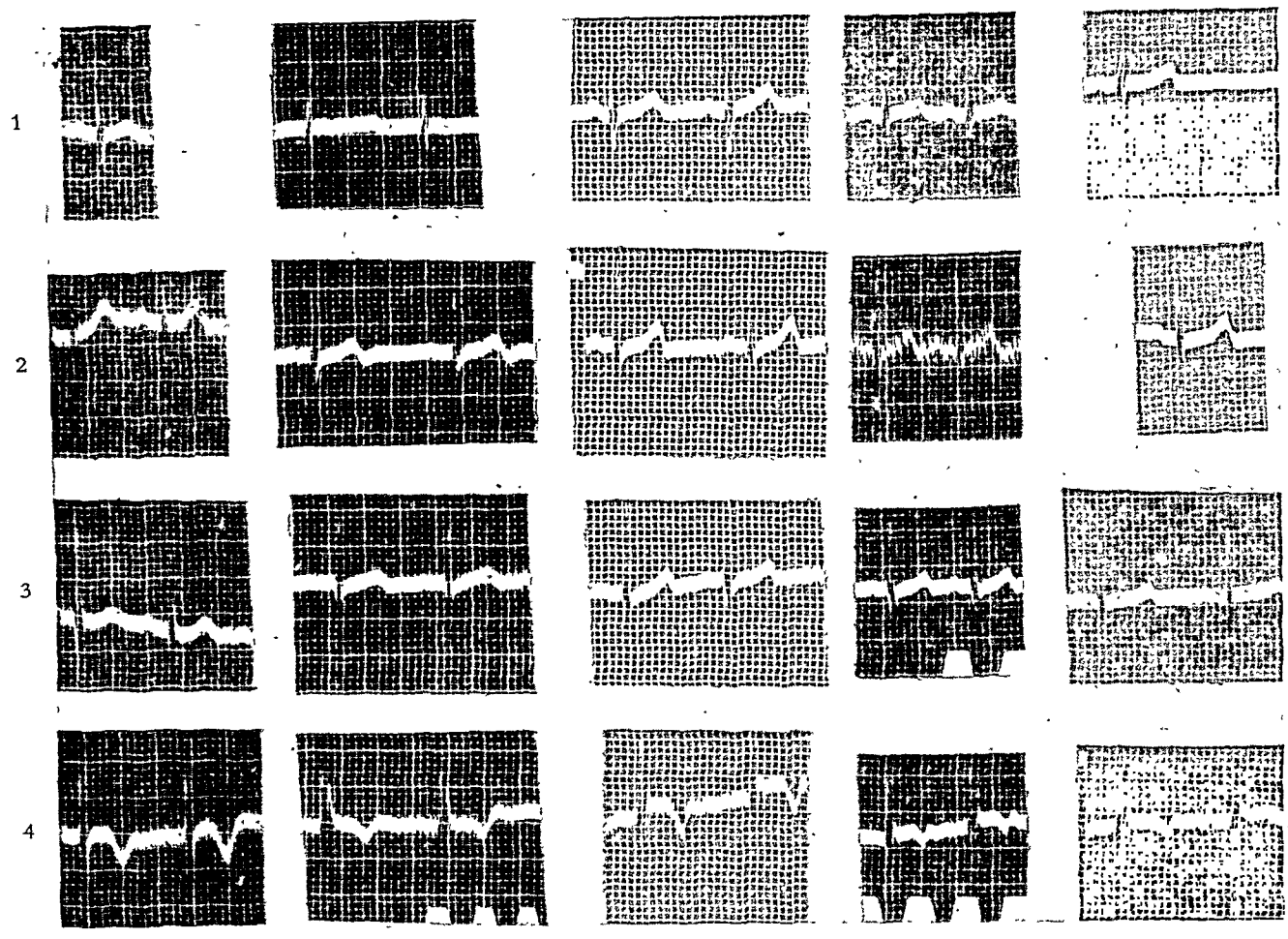


FIG. 2. RST segment and T wave changes suggestive of acute infectious myocarditis (nonspecific) complicating primary atypical pneumonia in a five-year-old male. Sudden onset of precordial pain, increased breathlessness, palpitation, weakness first apical sound followed by asthenia and persistently elevated sedimentation rate. These changes occurred during the stage of pneumonic resolution.

The two cases of acute infectious myocarditis are described in Figures 2 and 3. A marked secondary anemia with the red cell count rapidly falling below two million developed during the course of the disease in one patient, but this may have been due to sulfonamides. Following the onset of pneumonia, thrombophlebitis of the leg with secondary pulmonary embolism resulted in another case. Heparin therapy was instituted without recurrence.

DURATION OF ACUTE ILLNESS

The acute phase of disease was reckoned not to include the prodrome or period of involvement before entering the hospital. The active period of disease (exclusive of the convalescent interval) ranged from two to 73 days with an average of 10.1 days for the entire series. Because he sought hospitalization toward the end of a mild pneumonic process, one patient spent only two days of his acute illness abed. The higher figures, of course, occurred with patients suffering serious complications such as empyema. The average total hospital stay for pneumonia cases in federal institutions is 31.1 days and in city-county hospitals only 13.4 days.[13] These figures included the convalescent period. The average total hospital stay in our series was 28 days.

DURATION OF CONVALESCENCE

Because of the necessity of returning to full active duty, a longer period of convalescence was indicated. The maximum stay was afforded those with most marked postinfectious asthenia or complications. Residual symptoms, such as persistent dry cough, necessitated a further ambulatory period in the hospital. The convalescent period ranged up to a maximum of 75 days with an average of 17.9 days for the entire

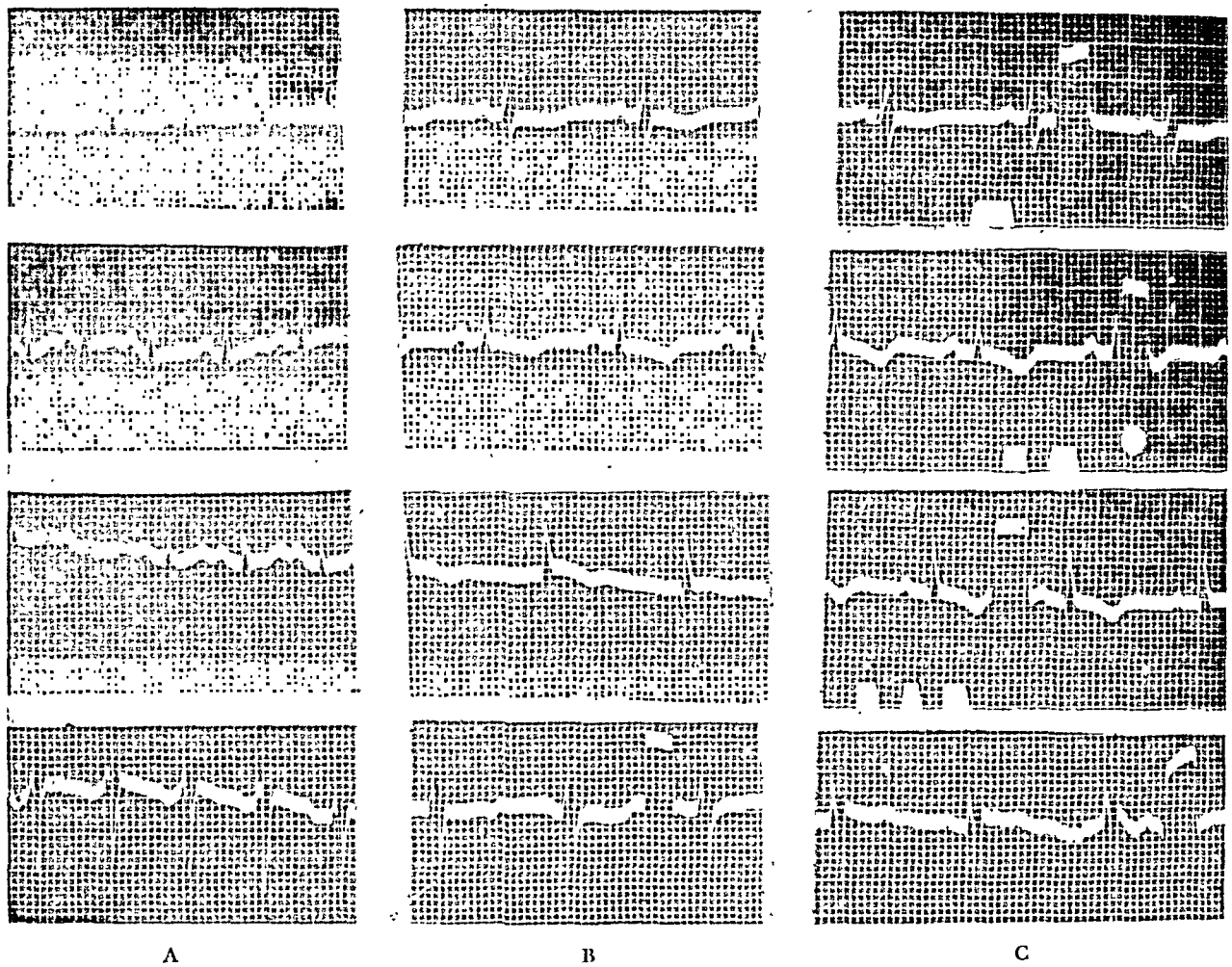


FIG. 3. Case of nonspecific acute infectious myocarditis. A. (Jan. 3) Rate 135. PR interval 0.14 second. Sinus tachycardia. Low voltage and slurring QRS complexes. T wave negative in lead 1 and low voltage remaining leads. Slight ST segment changes. No digitalis was given. B. (Jan. 8) Superimposed digitalis effect. Rate 72. PR interval 0.16 second. Elevated RST segment lead 3. C. (Jan. 11) Superimposed marked digitalis effect. Rate 68. PR interval 0.16 second.

series. An organized program was available for reconditioning. It began with mild and stimulating exercises which were increased to suit the patient's tolerance through four graduated classes. It was found to decrease the convalescent period because of more rapid physical improvement, improved morale and decreased frequency of psychoneurotic states induced by prolonged hospitalization. A doctor was specially assigned to check for relapses, individual progress and class advancement.

TREATMENT

Symptomatic Treatment. Patients were kept in bed until the lungs were clear on serial x-ray study since elevated sedimentation rates and mild symptoms persisted on many occasions.

Adequately trained nursing care in special pneumonia wards was considered important in the management of pneumonia cases. Symptomatic treatment included expectorants with and without codeine, steam and benzoin inhalations for severe dry coughs, analgesics for headaches and generalized aches, adequate fluid intake, gargles for pharyngitis and alcohol sponging for temperatures above 103° F. Symptomatic care was employed exclusively in 98 cases of primary atypical pneumonia and also as indicated in conjunction with specific treatment. Continuous oxygen was necessary in nine cases to combat severe dyspnea and cyanosis.

Specific Therapy. Whereas the status of specific therapy in pneumococcic pneumonia is well established, considerable controversy exists as to its value in primary atypical pneumonia. The consensus at present is that it is of no value. Admittedly, there is little or no specific effect on the virus itself. Some investigators[6] feel that specific therapy should be employed only if there is secondary invasion by pyogenic bacteria as manifested by increasing numbers

of pyogenic organisms in the sputum, abrupt rise in leukocyte count, chills and fever and evidence of roentgenographic spread.

Specific therapy was employed in 342 cases, 262 of which were treated with the sulfonamides, 62 with penicillin and 18 with combined specifics. It was concluded from the low incidence of complications in our series that secondary invasion and spread was kept at a minimum. Specifics may have greater significance in the years when pulmonary infections appear more virulent. Reactions from their use were inconsequential and no serious effects were recorded with one possible exception. Specific therapy may have reactivated a chronic glomeronephritis in one case. However, it is more likely that this complication was a response to the toxemia rather than sulfonamides.

Blood Transfusions and Plasma. A most important adjunct to the treatment of massive involvement in primary atypical pneumonia was repeated small whole blood transfusions which avoid overloading the right heart. The blood was drawn from convalescent cases on the ward and carefully cross-matched. A remarkable response was noted in cases that appeared dangerously ill or moribund (Figs. 4, 5, 6, 8). The blood supplied antibodies of high titer to combat the infec-

FIGURE 4 (*Right*)

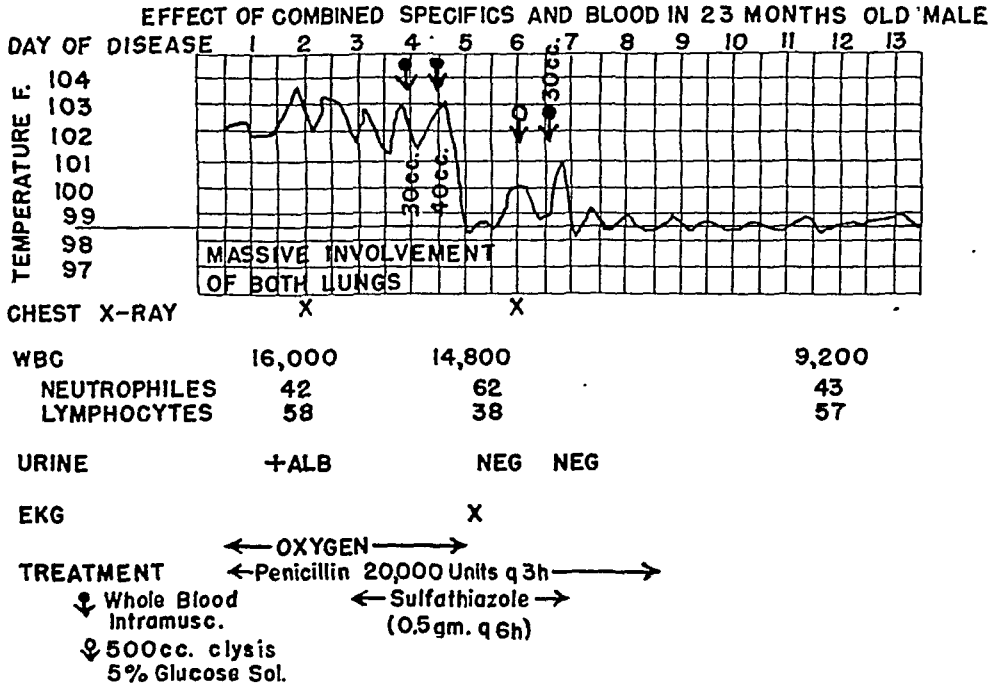
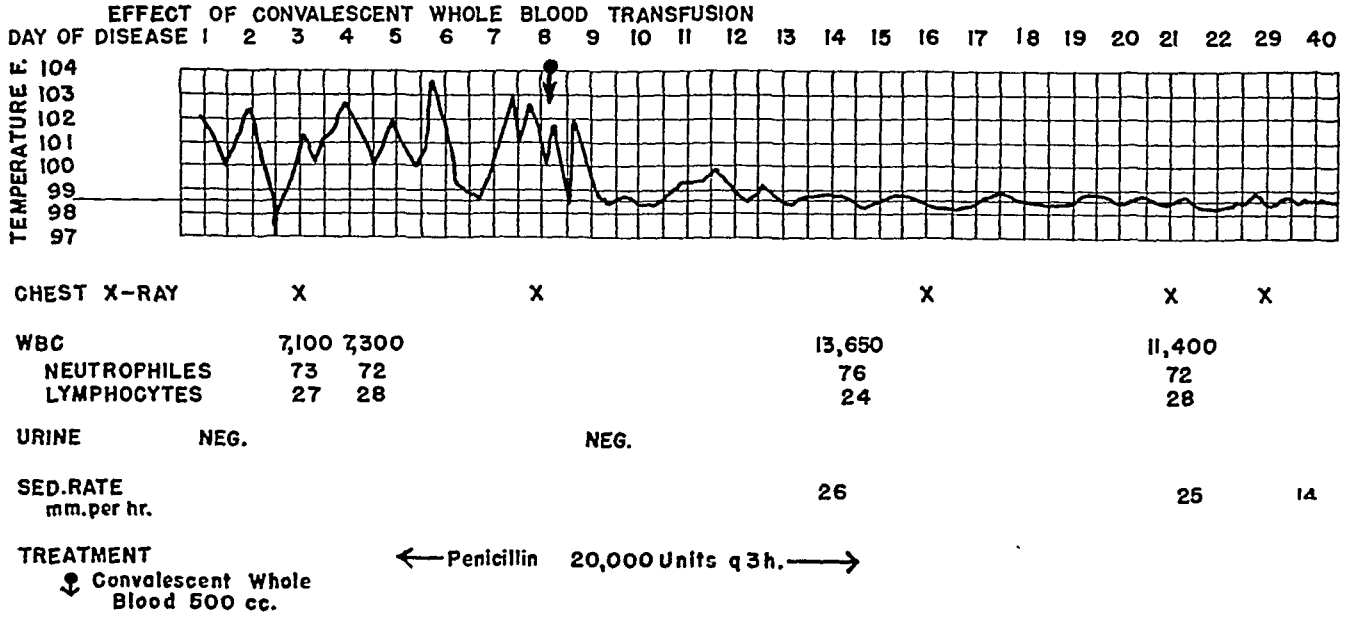


FIGURE 5 (*Below*)



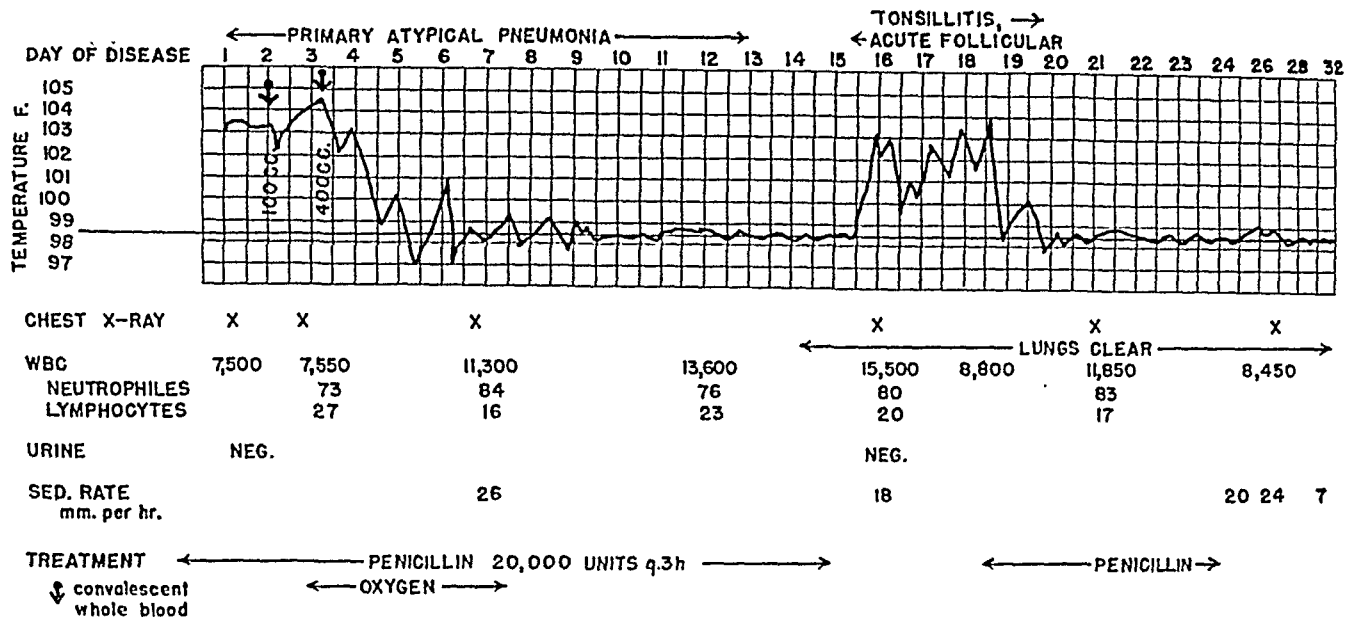


FIGURE 6

tion, severe dyspnea and signs of impending vascular collapse. Fifteen transfusions (250 to 500 cc.) of whole blood were supplied for ten cases. The average amount transfused was 300 cc. Favorable temperature and general physical response was noted in every case. Plasma (500 cc.) was employed to combat peripheral vascular collapse until whole blood was made available on two occasions.

COMPARATIVE STUDY OF SPECIFIC THERAPIES

In the appraisal of the effectiveness of the various methods of treatment it is well to remember that specifics were employed only in patients that were severely ill. Transfusions of convalescent whole blood were employed as a supplementary measure in a few advanced cases with dramatic results. Symptomatic treatment alone was instituted in the milder cases. The appearance of complications or progression of the disease always called for more intensified efforts.

The duration of the illness and convalescent period in the more serious cases treated with specific closely approached the milder cases receiving symptomatic treatment only, thus indicating their therapeutic importance. (Table 2.) The average for the period of acute illness was approximately ten days in each of the sulfonamide, penicillin and symptomatic groups. Penicillin appeared to be slightly more effective than the sulfonamides as indicated by the abbreviated convalescent period which was shortened by an average of almost five days.

Combined sulfonamide and penicillin therapy was employed 18 times in the most seriously ill cases. The acute and convalescent phases were prolonged in view of the severity of the illness. It is our impression that combined therapy is unnecessary in the average case and similar results are obtainable by employing either of the specifics.

Since transfusion of convalescent whole blood was used as an adjuvant in dangerously ill cases only, the average period of the acute phase compared favorably even with the milder cases receiving symptomatic treatment only. It was our impression that several moribund patients probably would have expired without its benefits. In dangerously ill patients with massive involvement of both lungs, intensified treatment com-

TABLE 2

Comparative Study of Therapies

TREATMENT	CASES	DURATION OF ACUTE ILLNESS (days)			CONVALESCENT PERIOD (days)		
		Average	High	Low	Average	High	Low
Sulfonamides	262	10.7	43	7	18.4	65	2
Penicillin	62	10.3	26	6	13.5	31	2
Combined sulfonamides and penicillin	18	17.2	73	8	23.7	46	2
Symptomatic	98	9.9	33	2	14.6	41	4
Supplementary convalescent whole blood	10	14.7	21	9	26.2	46	2

bining both specifics with transfusion is indicated (Fig. 4).

Cases Demonstrating Favorable Response to Convalescent Whole Blood Transfusions

CASE 1: *A white male, aged 18, was admitted with* a diagnosis of nasopharyngitis. After symptomatic treatment for two days, he was discharged as improved. This was apparently the prodromal period of his subsequent attack primary atypical pneumonia since he was readmitted a week later (Jan. 6) with severe cough.

Present Illness. The patient developed chills and fever accompanied by a sore throat the night before readmission. He had no headache or malaise but became easily fatigued and had severe nonproductive cough.

Physical examination revealed a well developed, well nourished white male appearing acutely ill. Temperature was 102° F., pulse 100, respirations 20, blood pressure 120/80. Complete physical examination was negative except for enlarged tender anterior cervical nodes. The tonsils were hypertrophied with slight infection. Remainder of the examination was negative.

Laboratory Studies. On admission there was a white blood count of 7,100 with a differential of 73 per cent neutrophiles and 27 per cent lymphocytes. Urinalyses were persistently negative. The sedimentation rate varied from 26 mm. per hour on admission to 14 mm. on date of discharge.

Chest film taken four days after admission revealed an area of markedly increased density of the left upper lobe, typical of a prime atypical pneumonic process. *Five days later a chest film showed no appreciable alteration in its extent.* Another x-ray taken on January 28 revealed slight improvement. A film on February 8 finally showed complete resolution.

Course and Treatment. The patient was given penicillin for four days (20,000 units intramuscularly every three hours) but his temperature remained around 102° F. He developed a severe cough and chill on January 10 but physical findings were negative. On January 15 his temperature remained elevated at 102° F. and crepitant râles were heard in the left midlung area anteriorly. The patient received 500 cc. of whole blood from a convalescent case. This was given because of toxicity and progression of pneumonic involvement, determined by serial roentgenograms, in spite of adequate penicillin therapy. There was an immediate drop in temperature from 101.5° F. to 99° F. within six hours following transfusion. However, it rose again to 102° F. during the night. The next morning the temperature returned to 99° F. and remained normal until the time of discharge (Fig. 5). On January 19 there were no abnormal physical findings. Roentgenogram showed complete clearing of the lungs on February 8.

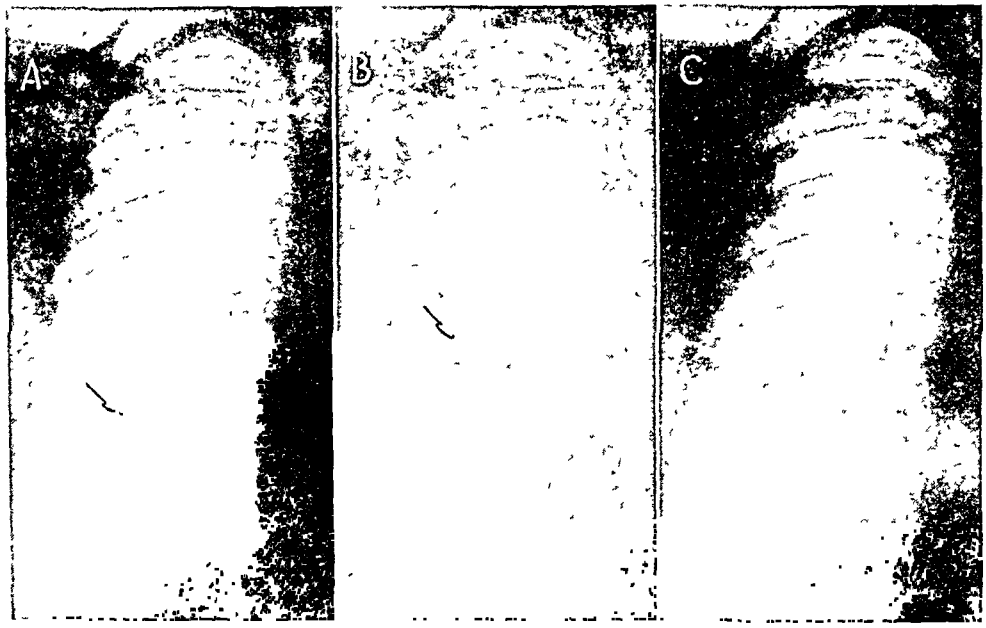


FIG. 7. A. Area of consolidation with central zone of radiolucency resembling lung abscess on admission. B. Extension of pneumonia process with absence of clear central zone eight days later. The picture now resembles that of primary atypical pneumonia. C. Complete resolution of pneumonic involvement three and one half weeks later.

Figure 6 demonstrates a similar response to transfusion and penicillin in another case with massive involvement.

INTERESTING MANIFESTATIONS OF PRIMARY ATYPICAL PNEUMONIA

In this series of 440 cases, several unusual manifestations of primary atypical pneumonia occurred. These were of sufficient interest to present in detail since they illustrate the occasional occurrence of unusual complications which may add to confusion in diagnosis.

Case Resembling Lung Abscess

Case 2: A white male, aged 21, was admitted on May 30 with a nonproductive cough.

Present Illness. Patient had a nonproductive severe cough for the past three or four days. He became progressively weaker and developed anorexia. He had generalized aches and became fatigued easily. There was no bloody sputum, foul odor to the breath or purulent expectoration. There was no history of previous lung disease.

Physical Examination. Temperature was 98.6° F., pulse 68, respirations 19. Patient was a well developed and well nourished white male, not acutely ill. Complete physical examination was negative except that the right chest showed marked limitation of motion on deep inspiration, and there was slight dullness with increased breath sounds and coarse râles confined to the right base posteriorly.

Laboratory Studies. White blood count was 10,100 with 70 per cent neutrophiles and 30 per cent lymphocytes. Urinalyses were repeatedly negative. Kahn test was negative. Repeated sputum tests revealed no acid-fast organisms. There were a few nonhemolytic streptococci found in the smears and culture. Hemoglobin was 97.5 per cent.

X-ray of the chest revealed a 4 cm. area of infiltration in the right lower lung field with streaking into the right hilar region. In the center of the infiltration there was a central area of decreased density (Fig. 7). These findings were suggestive of pulmonary abscess. The remainder of the right lung and the left lung were essentially negative. The heart was within normal limits. A chest film the following day was essentially the same except that the central zone of decreased density was no longer present. On June 6 there was a marked extension of the infiltrative process in the right midlung field as compared with the admission film and again the central zone of radiolucency was not seen. On June 10 the original zone of radiolucency was absent, but there were two small areas of relative opaqueness within the area of infiltration. On June 19, chest film revealed a marked decrease in the extent and density of the infiltrative process in the right midlung field. On June 24 the area of infiltration was about one-third its original extent. No definite signs of abscess formation were present. There was no period of profuse expectoration suggestive of rupture or emptying.

Course and Treatment. Penicillin therapy (30,000 units intramuscularly every three hours) was instituted. The highest temperature recorded was 101° F. On the fifth day of hospitalization he developed a sudden severe pain in the right chest and a small amount of blood-streaked sputum which continued for three days. On June 6 there was no evidence of pleural friction rub although the breath sounds were still diminished on the right side. On June 12, the chest revealed an occasional râle at the base poste-

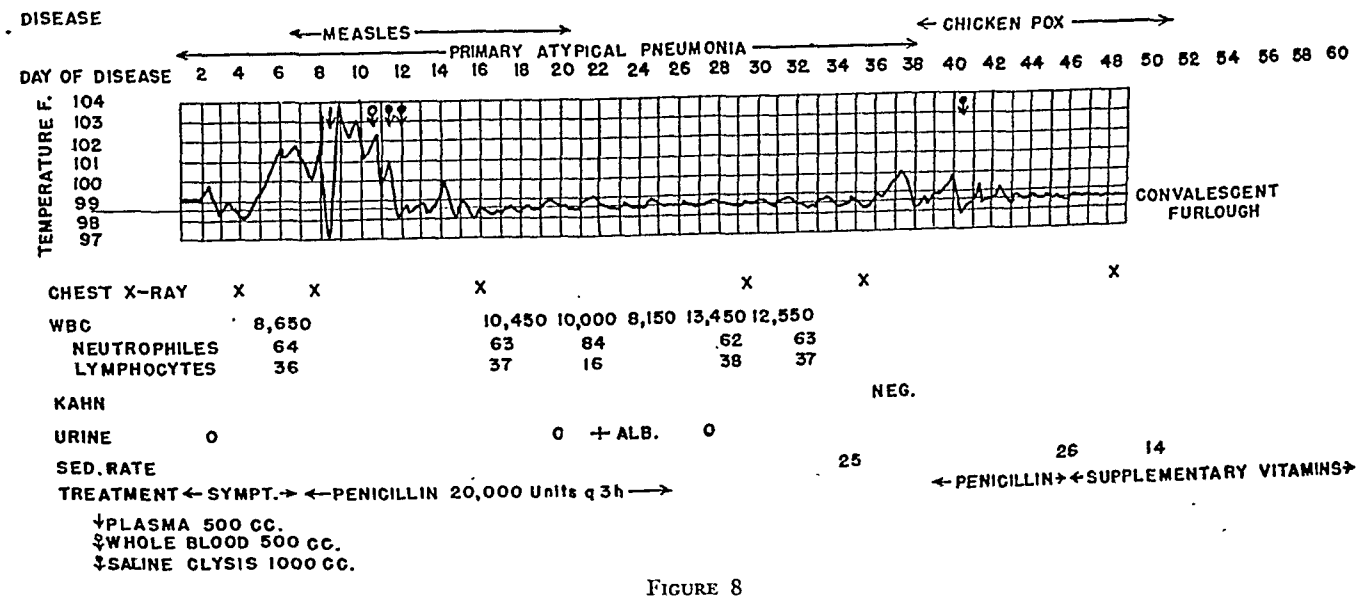


Figure 8

riorly, but normal breath sounds were audible. On June 17, a few coarse râles persisted in the right base posteriorly. On June 24, all abnormal physical findings disappeared.

Except for the initial roentgenogram which closely resembled a lung abscess, the history, clinical course and laboratory findings strongly suggested the presence of primary atypical pneumonia. The occurrence of blood-streaked sputum was not unusual in our series (among those with a productive cough 12.6 per cent were frankly bloody and 5.8 per cent were rusty). The pleuritic involvement was secondary to the pneumonia. There was no evidence of pulmonary infarction.

Case of Primary Atypical Pneumonia Followed by Measles and Chicken Pox

Case 3: A white male, aged 18 with two months' service, was admitted January 8 with a sore throat (Fig. 8).

Present Illness. Patient developed sore throat with fever the preceding day followed by a cough that was nonproductive.

Physical Examination. Temperature was 99° F., pulse 70, respirations 20. His face was flushed and the pharynx was mildly injected without cervical adenopathy. The lungs were clear to percussion and auscultation. The remainder of the examination was negative.

Laboratory Studies. Blood count on admission was 8,615 white cells with 64 per cent neutrophiles and 36 per cent lymphocytes. Three days later the white count rose to 12,550 with a differential of 63 per cent neutrophiles and 37 per cent lymphocytes. Repeated urinalyses were negative except for one plus albumin on one occasion. Sedimentation rate on admission was 25 mm. per hour. Because of the rising temperature and occasional râles, a chest film was taken ten days after admission and an area of infiltration was noted at the right base. The heart was within normal limits.

Course and Treatment. The patient was treated symptomatically for nasopharyngitis for the first four days. He then developed a temperature of 100° F. and occasional râles appeared at the right base. He was placed on penicillin therapy (20,000 units every three hours). His temperature climbed steadily to 104° F. on the third day after the diagnosis of primary atypical pneumonia was established (Jan. 15). Convalescent whole blood (500 cc.) was given on the tenth day of illness and there was an immediate drop in temperature to 100° F. which then subsided to normal levels. At the height of the temperature a diffuse morbilliform rash developed on the forehead, arms and trunk. This was diagnosed as measles by several observers. The rash finally disappeared on January 30. Temperature at this time was 99.4° F. He was maintained on penicillin and on February 21 the patient developed chicken pox on the trunk and face. On February 24 the patient became afebrile and asymptomatic. On March 8 the individual lesions were completely encrusted. On March 10 there was complete disappearance of all crustation. He remained in the hospital for an additional convalescent period of 11 days. Because of marked postinfectious asthenia, a convalescent furlough of two weeks was granted.

Although there was no question about the existence of chicken pox, some question may be raised as to whether the measles rash was a reaction to penicillin. The concurring opinion of several observers, the skin clearing despite continuance of full doses of penicillin and the subsequent clinical course militate against an allergic type of response. In addition, an epidemic of measles was prevalent at the time, to which he was probably exposed.

Case with Meningismus, Old Pleuropericardial Adhesions and Severe Postinfectious Asthenia

This case is of interest because of several confusing features. Because of severe occipital headache and neck stiffness on the second day, a meningeal complication of the pulmonic infection was suspected. A spinal tap proved to be negative. Subsequently, sharp intermittent pains at the cardiac apex, weakness and shortness of breath suggested pericardial involvement. Serial x-rays (Fig. 9), fluoroscopic study and serial electrocardiograms (Fig. 10) demonstrated the presence of dense pleuropericardial adhesions of long standing. A diagnosis of postinfectious asthenia seemed most probable.

Case 4: A white male, aged 33, was admitted February 2, 1946.

Present Illness. Patient developed sore throat, chills and fever, severe cough, headache and chest pain two days prior to admission.

Physical Examination. Temperature was 102° F., pulse 112, respirations 25. He had an injected pharynx and breathing was somewhat labored. Lungs revealed dullness and crepitant râles in the right anterior chest. Heart showed no evidence of enlargement, murmurs, thrills or friction rubs. The heart tones were of good quality. Blood pressure was 110/70. The remainder of the examination was normal.

Laboratory Studies. The white blood count was 7,850. Sputum revealed a few lancet-shaped diplococci and short-chained streptococci. Urinalyses were

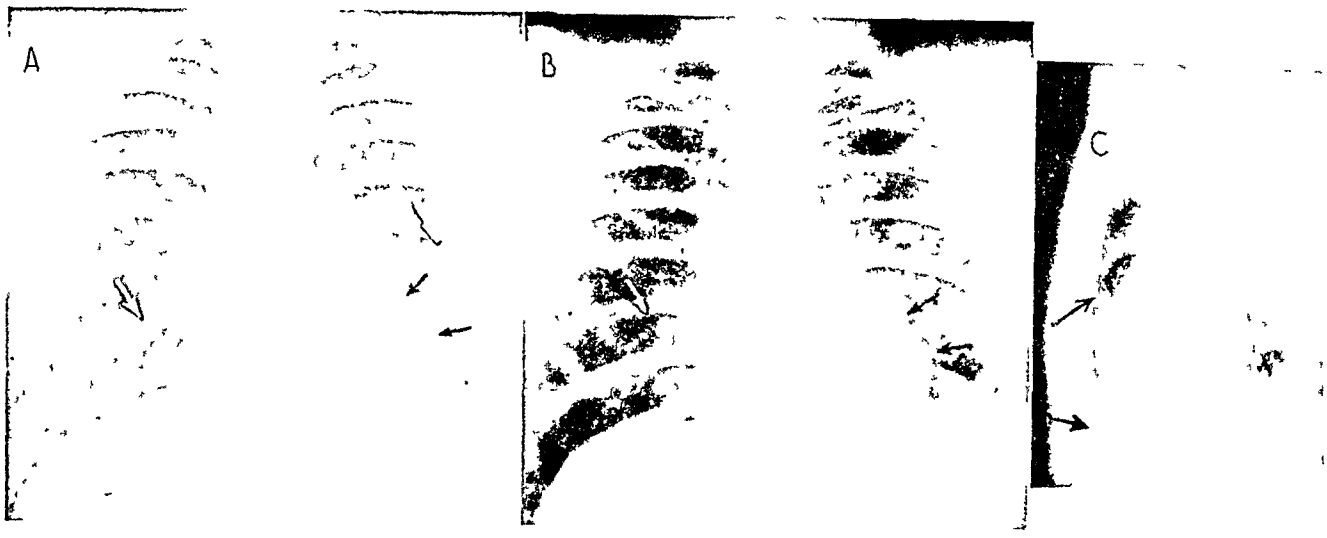


FIG. 9. A. Primary atypical pneumonia involving the right cardiophrenic area (beneath the white arrows). B. Resolution 16 days later. Black arrows point to marked old pleuropericardial adhesions. Note persistent elevation of left diaphragm, scalloped left heart border and retraction of heart to left. C. Lateral view showing obliteration of precordial area by dense adhesions.

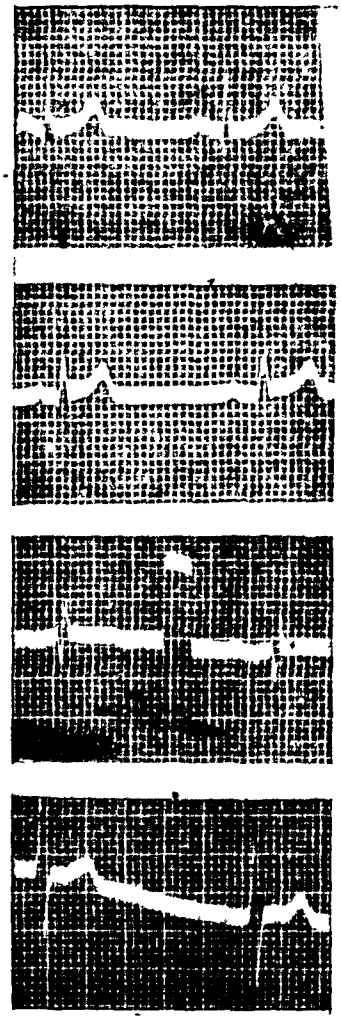


FIG. 10. Regular sinus rhythm. Rate 60. PR interval 0.16 second. Decreased voltage and slurring QRS complexes in limb leads. Deep Q in lead 3. RST segment elevated in leads 2 and 3 Low voltage T wave in lead 3. Frequent serial studies revealed no change in electrocardiograms. The tracings were compatible with the clinical and x-ray diagnosis of old pericardial adhesions.

normal on several occasions. Sedimentation rate ranged from a peak of 13 mm. per hour to 9 mm. per hour at the time of discharge. Spinal fluid cell count showed three lymphocytes and total protein of 32.4 mg. per cent. The smears and culture were negative. Serial x-ray studies (Fig. 9) showed both bases to be involved by primary atypical pneumonia which cleared completely 16 days later. X-rays and fluoroscopic examination of the heart showed the left border of the heart to be scalloped in three wide curves strongly suggestive of pleuropericardial adhesions. The heart was drawn toward the left side. Pulsations were somewhat diminished and the outlines did not change with position.

Serial electrocardiograms revealed an unchanging picture (Fig. 10). The circulation time (calcium gluconate) was 15 seconds. Venous pressure was normal.

Course and Treatment. On admission the findings were suggestive of meningeal involvement. The spinal tap revealed normal findings indicating a probable meningismus. Patient was started on penicillin therapy (30,000 units every three hours, intramuscularly) and placed in an oxygen tent. On February 28, cardiac consultation revealed no evidence of pericardial fluid, chronic adhesive pericarditis, Pick's polyserositis or constrictive pericarditis. It was concluded that the patient was not incapacitated by any cardiac pathology but that the residual symptoms were due to a severe postinfectious asthenia secondary to primary atypical pneumonia.

The patient ran a temperature up to 102.2° F. for two days and then with penicillin and sulfadiazine it gradually subsided within four more days.

CASE WITH SECONDARY MASSIVE EFFUSION

CASE 5: A white male, aged 29, was admitted July 16 with a chief complaint of slight weakness and pain in right chest for one week which was aggravated by

deep breathing. He developed a cough and had a slight chill and fever the day of admission. Past history was noncontributory.

Physical examination revealed râles with flatness and slightly diminished breath sounds at the right base.

Laboratory Studies. Urinalyses were consistently negative. The sedimentation rate ranged from 35 mm. per hour to 25 mm. per hour. Red blood count was 4,600,000 cells with 94 per cent hemoglobin. White blood count was 9,500 with 87 per cent neutrophiles and 13 per cent lymphocytes. The highest recorded white blood count was 10,650. X-rays on admission showed an area of dense sharply defined

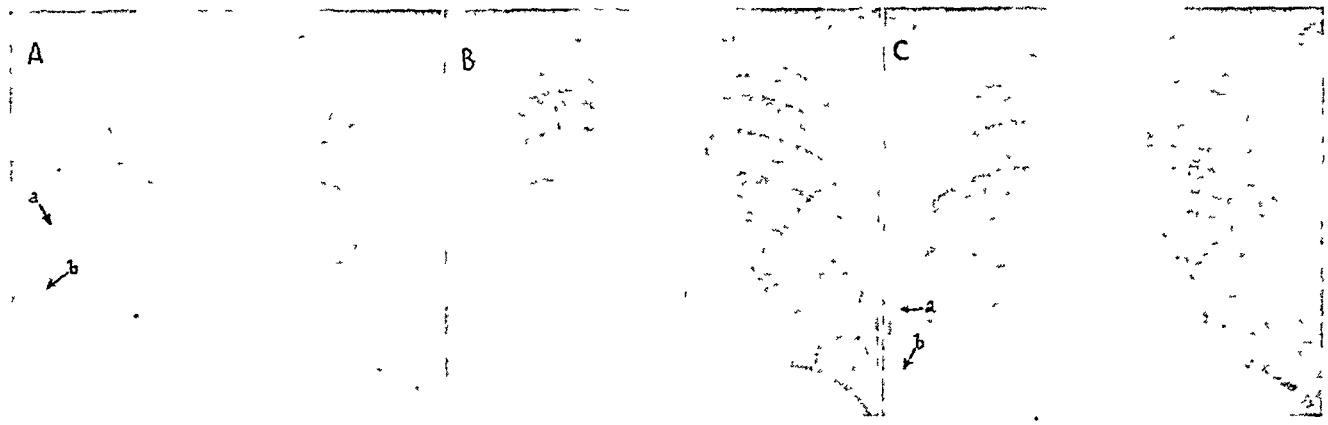


FIG. 11. A. Pneumonitis with marked pleural reaction despite paucity of complaints and findings. Thickened interlobar pleura at (a) with fluid at (b). B. Marked progression one week later. C. Pneumonic resolution with residual increased pulmonary markings two weeks later. Obliteration of costophrenic sinus at (b) and thickened visceral pleura at (a).

radiolucency at the right base with extension upward into the axilla having the appearance of fluid. There was a mottled appearance of the underlying right middle and lower lobes indicative of primary atypical pneumonia. The remainder of the lung fields and cardiac silhouette were normal (Fig. 11).

On July 19, another x-ray revealed further progression of the pneumonic infiltration of the right middle and lower lobe with an increased accumulation of fluid. On July 22, definite evidence of regression of the pneumonic infiltration was apparent. However, about one-third of the lower right lung field remained affected. The pleura appeared somewhat thickened above the area of consolidation. On July 26 and 31 there was further resolution of the process. The right cardiophrenic angle remained obliterated by a small amount of residual fluid at the time of discharge. Chest tap was not performed.

Clinical Course. The patient was immediately placed on penicillin therapy (20,000 units every three hours) and the initial temperature of 100.8° F. subsided at once. He was free of all chest pain two days following admission. All clinical findings of pneumonia disappeared on the fifth hospital day. The patient was hospitalized for a total of 24 days. The final diagnosis was primary atypical pneumonia with secondary massive pleural effusion.

DISCUSSION

Primary atypical pneumonia probably occurs much more frequently than is suspected. In the armed forces it occurs in approximately one person per hundred per year but its actual incidence in civilian populations is undetermined.[14] Because of the unestablished etiologic agent or agents, gradual and ill-defined prodrome, indefinite and variable physical signs and nonspecific laboratory aids, the diagnosis is usually difficult to establish without roentgenographic corroboration. It is hoped that our study of 440 cases proved by serial roentgenograms may be of value in directing attention to the importance of x-ray examinations in establishing the early diagnosis of suspected cases. Contrary to the prevailing consensus, the use of specific therapy is indicated only in selected cases which show suspected or proved secondary invaders, massive or progressive involvement, marked toxemia, cyanosis and dyspnea, or complications, such as pleural effusion. The sulfonamides produced very few reactions. Penicillin is slightly more effective, but must be given in adequate dosage. Reasons for the perfect mortality rate of this series are dependent on other factors. Most of the cases occurred in young people, previously in excellent health. Since the patients could not continue on a full duty status, earlier hospitalization and treatment was imperative. Convalescence in a well regulated physical reconditioning program and convalescent furloughs combatted the tendency to post-infectious asthenia, recurrence of pulmonary involve-

ment and the psychoneurotic states. The employment of serial x-ray studies was by far the most important method of following the progress of the pulmonic involvement. Adjuvant therapy during the convalescent period included vitamin supplements, iron preparations, high caloric diet and adequate periods of rest. Selected cases showed excellent response to whole blood transfusions from convalescent patients. They were of great value in dangerously ill or moribund cases. Transfusion was especially important when the sulfonamides and penicillin failed to have effect on secondary invaders or rapid progression of the disease. Finally, adequate nursing care by a specially trained staff on special pneumonia wards was an important factor in reducing morbidity.

SUMMARY

1. A study of the diagnosis and treatment of 440 cases of primary atypical pneumonia with no fatalities over a three-year period, is presented.

2. Despite some reports to the contrary, a definite prodromal stage averaging four days was found to occur. The prodrome is most frequently mistaken for an upper respiratory infection.

3. Because of the gradual and ill-defined prodrome, indefinite and variable physical signs and nonspecificity of laboratory aid, early diagnosis can be definitely established and the clinical course more accurately gauged by serial roentgenographic studies.

4. The sulfonamides or penicillin are indicated in adequate dosage in selected cases showing evidences of progressive or massive pulmonary involvement, suggestive or proved presence of secondary invaders or signs of severe toxemia, dyspnea and cyanosis. Penicillin is slightly more effective and is accompanied by fewer reactions than the sulfonamides. Combined specific therapy is unnecessary unless the patient is dangerously ill.

5. Whole blood transfusions from patients convalescing from primary atypical pneumonia are of great value in supplying antibodies of high titer in dangerously ill cases.

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Acute nephritis, somewhat like rheumatic fever, remains one of the diseases which, despite a probably high recovery rate, always carries a threat of serious, crippling, chronic and eventually fatal illness. It is the more dangerous because it may be mild and insidious though easily detectable if careful study is made. The author stresses diagnosis and proper handling of the acute or initial phase.

The Problems of Acute Nephritis and Its Sequelae*

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The onset of acute glomerulonephritis may be abrupt and stormy or insidious and mild. If all patients presented the typical textbook picture of albuminuria, hematuria, hypertension, and edema, the recognition of acute nephritis would be comparatively simple, but such is not the case. Many times the acute phase starts in a mild manner without the characteristic symptoms, and only slight albuminuria, few casts, and microscopic hematuria are present. Such cases often pass unnoticed, untreated, and terminate eventually in chronic glomerulonephritis, from which the patient never recovers.

Although the opinion is not unanimous that chronic nephritis always evolves from an acute attack which fails to heal completely, this concept is more widely held now than ever before. The recognition and treatment of the acute phase, whether it is mild or severe, are the chief measures for prevention of the chronic form of the disorder.

THE EARLY PHASE

The diagnosis of acute nephritis is usually easy to make, but it is often missed because it is overlooked. Difficulty arises occasionally in determining whether the disorder is an acute nephritis or an acute flare-up of a chronic nephritis. As the prognosis is quite good in the acute type and definitely bad in the chronic, the diagnosis is of more than academic interest. In coming to the proper decision, a careful history, a study of the specific gravity of the urine, and a red blood cell count are the most useful aids. Usually, the specific gravity of the urine tends to be normal or higher in acute nephritis, while in the chronic form, it is fixed at a lower level than normal. The presence of a definite anemia points more to chronic nephritis, because anemia is rare in the acute form.

It is becoming more widely recognized that mild forms may exist, pass undiagnosed and untreated, and progress into the chronic stage before it is realized that the kidneys have become damaged beyond the possibility of repair. In a study of 94 cases of acute glomerulonephritis, with special consideration of the stage of transition into the chronic form, Murphy et al.[1] emphasized the need for careful consideration of the milder forms of the disease. By a follow-up study, these authors showed that the milder forms are as dangerous as the more severe types in respect to the remote prognosis. Bell [2] confirmed this concept and stated that there are innumerable transitions between subclinical glomerulitis and clinical acute nephritis. Fundamentally, the same type of reaction occurs in the two forms; the difference exists only in the intensity of the disease.

As in the chronic form, there are five syndromes which must be considered clinically in dealing with acute nephritis. They are: (1) the urinary syndrome, (2) hypertension, (3) edema, (4) azotemia, and (5) uremia. All of these syndromes are not, or need not be present at the same time; some are variable and transitory. One may develop and dominate the clinical picture for a time and then disappear temporarily or permanently. In an investigation by Murphy and Rastetter [3] in 1938, an analysis of the clinical syndromes and progress which occurred in 150 patients with acute glomerulonephritis was made. The results of this study are as follows:

SYNDROME	NUMBER OF PATIENTS	PERCENTAGE
Urinary	150	100
Hypertension	60	40
Edema	86	57.3
Azotemia	66	44
Uremia	10	6.6

It is the urinary syndrome that is of most importance in diagnosing acute glomerulonephritis, as it is always present, is the most accessible to detection, and

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Presented at the American College of Physicians 28th Annual Session, Chicago, Illinois, April 30, 1947.

is the least likely to be misinterpreted. The study of the urinary syndrome alone is worthy of more thought, because often the examination of the urine is neglected unless other evidences, such as hypertension, edema and hematuria are found.

Formerly, hypertension was considered a constant feature in those patients suffering from acute glomerulonephritis, but today it is generally accepted that hypertension may be lacking throughout the entire course of the disease. However, its onset in the course of acute nephritis is significant in that it is always a discouraging and sinister event, and it is usually indicative of an unhealed renal lesion. But the seriousness of hypertension relates not so much to the renal inflammation as to disturbances in the function of the heart. Myocardial disease may develop and produce either heart failure, tachycardia, palpitation, or pulmonary edema. However, opinion of the importance of the role of myocardial insufficiency in acute nephritis varies among clinicians. Cecil [4] states that heart failure is the commonest cause of death in acute nephritis. Levy [5] and Murphy, Grill and Moxon [6] discussed cases of acute nephritis in which heart failure occurred without hypertension, and in 1937, Master, Jaffé and Dack [7] found cardiac insufficiency to be common in a series of 24 cases, and at times to be severe enough to cause death. Recently, Burke and Ross [8] reported a series of 90 children's cases in which only three cases of heart failure were not accompanied by significant blood pressure elevation.

The presence of hypertension should alert one to the danger of cerebral edema which may cause the convulsions or so-called "convulsive uremia." The convulsions are not related to renal insufficiency, but are the result of high blood pressure. The sequence of events is nephritis, arterial hypertension, increased intracranial pressure due to edema of the brain, and convulsions. The presence of hypertension becomes one of great importance, therefore, in the study of acute nephritis.

But whatever part hypertension may play in the clinical picture, it is certain that it is the most important feature in making a prognosis. If hypertension exists, the prognosis is bad; if there is no hypertension, the prognosis may be unfavorable, but the chances of complete cure are good.

Edema is the syndrome which gives most concern to the laity, but to the physician, it is probably least important of the five syndromes. Its importance lies in the fact that it is often the first feature to attract attention and show that something has gone wrong; that there probably is an involvement of the kidney. Edema gives the patient a bloated appearance around the eyes and a roundness and fullness to the face as well as contributing to the characteristic pallor which is frequently an early feature of acute nephritis. Generally, edema is not looked upon as a grave sign unless it occurs in the period following the first few weeks of acute nephritis. At that time it is evidence that the nephritis is becoming degenerative or subacute, and its prognostic significance is important.

Edema is not always localized to the face and around the eyes. There may be a generalized anasarca which is very pronounced in the early stages. Sometimes the edema occurring with acute nephritis is not due to the kidney lesion at all but is due to circulatory disturbances accompanying hypertension and heart failure. The relationship of the edema to the lowering of the plasma albumin has been debated. Personal experience proves definitely that the edema of acute nephritis may occur without the reduction of plasma albumin. The exact nature of the pathogenesis of edema of acute nephritis is a problem which has not been solved completely.

Like edema, azotemia, in the early periods of acute nephritis, is of little significance, but when it occurs after the first ten days, its presence causes concern because it indicates that the functional capacity of the kidneys is being reduced, and the prognosis becomes doubtful. Diagnostically, an estimation of the blood urea nitrogen is not of first importance, but prognostically, it is useful after the first ten days or two weeks of the disease, as is true of the edema syndrome.

Uremia, the last of the five clinical syndromes to be considered in acute glomerulonephritis, is a difficult one to evaluate because both the genuine and convulsive forms are embraced under the heading "uremia." Genuine uremia is the direct outcome of renal insufficiency. and is independent of the convulsive seizures which may be associated with it. It is entirely unrelated to hypertension and is usually brought on by an interference with the urinary output. Convulsive uremia, on the other hand, is identified by headache, visual disturbances, vomiting, apathy, and choked disks, and is usually associated and undoubtedly caused by hypertension.

THE COURSE

Acute nephritis may take one of four courses: (1) It may heal completely. (2) The patient may die in the acute phase. (3) The nephritis may become chronic. (4) It may pass into the so-called "latent period" and subsequently either heal completely or become chronic.

Less than 10 per cent of patients with acute glom-

erulonephritis die in the early acute phase. Renal insufficiency with genuine uremia may be the cause of death, but heart failure, or convulsions with or without heart failure may be the chief factors in bringing about early death.

Although most cases of acute glomerulonephritis recover within a period of six weeks, in some cases a complete healing of the kidney is not accomplished in such a short period of time. Sometimes the patient seems to be entirely cured, but the cure is more apparent than real. In an after-study of a large series of cases [18] it was found that while most patients recovered from the initial phase of acute nephritis, almost 27 per cent of the cases in that series developed chronic glomerulonephritis at a later date.

After the acute episode is over, a latent period may follow in which the patient may feel well. Upon a careful examination of the urine, however, one may find evidence of an inflammatory lesion in the kidney. The urine may contain albumin and an excessive number of red blood cells, white blood cells and granular casts. It is this transitional phase of the disease which is of great importance, since the ultimate fate of the patient may be determined by it. Snoke [9] considered that lack of proper consideration of this symptomless period was responsible for conflicting views on the prognosis of acute nephritis. My own experience verifies Snoke's statement. It is in this transitional period that the kidney may gradually heal completely or may progress into chronic nephritis. If the physician keeps in mind the above facts, the patient may be more carefully guarded against further infections as well as treated more energetically, and thus the catastrophic event of chronic nephritis may be avoided.

It is true that difficulty may arise in differentiating the latent period from the chronic state, since the latent period may evolve gradually into the chronic form. But, as a general rule, after a two-year period the disease may be classed as chronic. Addis,[10] the first to study the latent phase in a detailed manner, observed that patients may remain in it for as long as ten years apparently in perfect health but always with an abnormally high number of red blood cells and a few blood casts.

No one test has been found a reliable prognostic index in determining the degree of activity of the lesion in the kidney, but the results obtained from a combination of several measures may be used as a fairly accurate guide. Kidney function tests may be classed into the general and the specific. The specific tests, such as the inulin test for glomerular filtration and the diodrast for tubular activity, are not of the most importance in the study of acute nephritis. The general tests furnish all the information needed for the proper conduct of the case.

The tests which are particularly helpful are the dilution-concentration test of Volhard, the blood urea clearance test, the determination of the sedimentation rate of the erythrocytes, and the phenolsulfonphthalein test.

At times the dilution-concentration test appears to be of greater aid than the others, but to obtain an accurate prognosis one must not depend on this one test alone. A comparison of the prognostic significance of the urea clearance and dilution-concentration tests was done by Alving and Van Slyke [11] in 1934, and they concluded that the concentration test is more sensitive for qualitative detection of renal function; but for measuring the extent of renal damage, the urea clearance test is more accurate.

Also helpful in prognosis is the sedimentation rate of the erythrocytes. This test, however, must be repeated at frequent intervals, since a single determination may lead to false impressions. When the renal lesion is becoming quiescent, the rate falls; when the lesion is progressing, it is more rapid. The fact that the test is simple and easy to perform adds to its practical value.

The phenolsulfonphthalein test is one over which a cloud of criticism has hung. This test is nonspecific, but it is a simple, valuable method of obtaining general information regarding kidney function if it is performed with precision.

There are numerous other tests which have been advocated in the study of acute nephritis and its course, but with the exception of the quantitative study of the cellular elements of the urine by the method of Addis, they are redundant. An Addis count of the urinary sediment is of great value, not in determining the functional incapacity of the kidney but in determining whether the inflammatory lesion is healing or remaining active.

Prior to the use of these tests, latent nephritis was largely overlooked. However, within the last few years, the number of after-studies has steadily increased, and these observations are responsible for the modern concept of acute glomerulonephritis. Not all patients have the classical symptoms such as hematuria, edema, hypertension, and albuminuria, but milder forms are being recognized and treated adequately in increasing numbers today.

MANAGEMENT

As Volhard [12] pointed out years ago, the treatment of acute glomerulonephritis imposes a great responsi-

bility, but may also bring great satisfaction. He points out further that for the success of the treatment, the most important factor is that of time. While acute nephritis may commence abruptly with the features of hypertension, or acute renal or cardiac insufficiency, most cases do not. As Volhard [12] emphasized, there are cases of slow development in which the patient complains of headache, anorexia and fatigue, and then at times of even nothing at all. It is, therefore, necessary to be on the alert for acute nephritis after acute tonsillitis and other infections just as we formerly were accustomed to do after scarlet fever.

In acute glomerulonephritis, there is a generalized vascular involvement which may lead to a vasoconstriction of the kidney and of other essential organs of the body. Thus, treatment must embrace the entire body and not merely the kidneys.

The treatment of acute nephritis may be divided roughly into two periods: (1) The treatment of the early, stormy phase of the disease. (2) The treatment of the later milder stage. Only a comparatively small number of patients suffer from the acute explosive episodes of nephritis. In these episodes there are three chief dangers which must be combatted by energetic treatment. First, there is the danger of renal insufficiency followed by genuine uremia; second, the danger of convulsions which may cause death; and finally, the ever present danger of heart failure which may occur with or without the hypertension.

The hub of the treatment in this stage consists mostly in controlling the high blood pressure and promoting diuresis. By controlling the blood pressure, convulsive uremia and dilatation and failure of the heart may be forestalled. This may be accomplished by giving intravenously 3 Gm. of magnesium sulphate dissolved in 120 cc. of 5 per cent glucose solution. This may be repeated twice a day, or more often, depending upon the blood pressure and the general condition of the patient. If possible, it is well to determine precisely the level of the magnesium in the blood. There is always risk of producing respiratory failure when using magnesium sulphate intravenously, but the risk is greatly diminished by having on hand calcium gluconate for immediate use. In addition, the patient should be given sedatives, using phenobarbital or some of the other barbiturates. Digitalization may become necessary, especially when high blood pressure is present, because of the possibility of impending heart failure. Routine digitalization is not needed or recommended.

When oliguria or anuria occurs, uremia is imminent and unless the kidneys can be made to work again, death ensues. The daily limitation of the diet and fluids for several days to 800 cc. of sweetened fruit juices is an effective method of controlling the early edema, promoting diuresis and supplying a certain amount of carbohydrates. Sometimes the Karrell diet of 800 cc. of milk a day accomplishes the same results.

Frequently the patient is unable to take adequate fluid by mouth, and consideration must be given then to the use of intravenous fluids. When the disease has reached the stage where fluids must be given intravenously, the question arises as to what kind and how much fluid to use. Briefly, there are five kinds of fluids for intravenous use: (1) Whole blood, plasma or albumin to be used when there is severe anemia or when there is a reduction in the plasma proteins. (2) Physiologic saline solution. This may be used when there is hypochloremia or alkalosis. (3) The glucose solutions, 5, 10, and 50 per cent. The weaker solutions are used when there is dehydration and one wishes to replenish body fluids; the strongest solution is used when dehydration and diuresis are desirable. (4) Alkaline solutions, such as sodium bicarbonate, 5 per cent, and 1/6 molar sodium lactate solution may be used in the presence of acidosis. (5) Finally, one may use calcium chloride solutions or ammonium chloride solutions to combat alkalosis, if such should be present. In order to determine the kind of fluid to use, information should be obtained from blood analyses concerning the sodium and chloride levels, the carbon dioxide combining power, the plasma albumin-globulin ratio, and the hematocrit determinations. In the presence of impending heart failure, one must inject intravenous solutions very slowly, if at all. However, the anuria or oliguria point to the imminence of uremia, and the production of a diuresis is of vital importance. This requires the administration of fluid. As a rule, the danger of intravenous fluid to the heart depends more on the speed of the administration than upon the volume or kind of fluid administered. The presence of edema with oliguria does not contraindicate the injections of fluids. Saline solutions are withheld, of course, but glucose solutions may be used. When the blood pressure is high and the patient is twitching, one assumes that cerebral edema is present. Administration of some fluids would probably increase the edema and might make the patient's condition worse. However, 50 cc. of 50 per cent glucose solution may be given intravenously twice a day in order to bring about diuresis and reduce cerebral edema.

After the acute initial stage is over, or in milder forms of the disease, the following treatment may be used. (1) The patient should be kept at complete rest until the lesion in the kidney has become healed.

(2) The diet should be regulated and attention given to the protein, the salt, and the fluid intake.

The fundamental principle in treating acute glomerulonephritis is to obtain as complete a rest for the inflamed kidney as possible. In an investigation of 89 patients by Murphy and Peters [13] it was found that the 41 patients who were completely cured were those who remained in the hospital until well; the 48 who left the hospital before cure was accomplished fared less well eventually. Complete cure as early as possible is the goal.

True it is that enforced bed rest may be difficult in some cases, particularly in younger patients, but the need of it must be stressed by the physician if a complete recovery is desired. The rigidity exercised in carrying out this principle of rest is a matter to be settled in each case depending upon the conditions which prevail. If the progress is satisfactory and hypertension, azotemia, and edema have subsided, and the urine has cleared quite well, the patient may be allowed privileges after one month. A satisfactory routine for a few months, while waiting for healing to become complete, is to allow the patient bed, bathroom, lounge, and armchair privileges. After four or five months have elapsed and the patient is cured except for urinary changes, further enforced rest does not seem to be helpful. It is best then to consider the patient as an unhealed case of latent chronic glomerulonephritis. However, if hypertension or other syndromes persist, treatment must be continued on a firm basis, as the patient has become subacute or is actively chronic.

Physical inactivity serves to obtain rest for the circulation, lessens the demand for food and metabolic activity and materially reduces the work of the crippled kidney. Rest for the kidney is partially accomplished by regulation of the diet.

One must be guided somewhat by the patient's past food habits as well as by the condition of the kidneys in deciding the quantities of protein, salt, and fluids to be given. It is also to be remembered in therapeutics that while the kidneys must be considered primarily, the general condition of the patient must not be forgotten. As yet, there is no unanimity of opinion as to whether a high protein diet is injurious to patients with acute nephritis. From the experimental work of Addis,[14] Farr and Smadel,[15] and Chanutin and Ferris [16] it was agreed that the injured kidney heals faster when a low protein diet is given and slower or not at all when a high protein diet is maintained. On the other hand, Keutmann and McCann [17] found that a high protein diet did not retard healing and accelerated the return of renal function. Such observers as Volhard,[18] Fishberg,[19] and Stone [20] have said that the rigid restriction of salt, food (especially proteins) and fluids (except from 400 to 600 cc. of fruit juices) is advisable for three or four days. After this period, the quantity of fluid and food is gradually increased as required.

General opinion is that a diet containing 0.75 to 1 Gm. of protein per kilogram of body weight represents the optimal diet for the nephritic, since it fulfills protein requirements adequately and still does not retard healing of the kidney. The amount of fluid that should be given to a patient with acute nephritis varies according to the degree of renal insufficiency. When the kidney is unable to secrete the normal volume of urine, intravenous fluids must be resorted to for the promotion of diuresis, as the output of the urine depends upon the intake of fluid. If hypertension and edema of the brain with increased pressure of the cerebral spinal fluid or evidence of myocardial weakness are present, fluids must not be forced, for they may aggravate these complications. Edema is not a deciding factor either for or against the administration of fluids.

Regarding salt, it is best to rigidly prohibit salt for a few months. In the event that a hypochloremia develops, it can easily be controlled.

Sulfanilamide in the treatment of acute glomerulonephritis as yet has not been particularly spectacular. Rappoport, Rubin and Waltz [21] reported that it does not have any demonstrably bad effects on renal function, and they concluded that it appears to be without influence on the course and duration of acute glomerulonephritis. The place of penicillin in the treatment of acute nephritis is about the same as that of sulfanilamide.

The theory advocating the removal of infection in the treatment of nephritis is unsettled among clinicians, but most authorities believe such foci should be removed. Diseased tonsils, foci of infection in sinuses, apical abscess or abscess anywhere should be removed about one month after the passing of the acute episode. While statistics may fail to provide evidence of the benefit of such removal, the individual patient often shows striking benefit.

Structurally and functionally, the kidney is a very complex organ required to perform a variety of tasks. A disease of the kidney may depress certain of its normal activities at one period more than others. The management of acute nephritis, therefore, becomes a complicated affair, and proper results can only be achieved when the structural changes have been remedied and the alterations in the physiologic processes are corrected.

SUMMARY

1. The diagnosis of acute nephritis is usually easy to make, but it is often missed because it is overlooked. No difficulty would be encountered if the classical textbook picture of albuminuria, hematuria, hypertension, and edema were always present. The stumbling block is that there are mild forms of the disease which pass unrecognized, untreated, and finally develop insidiously into chronic nephritis from which the patient fails to recover. In differential diagnosis, the acute form must not be confused with an acute exacerbation of the already existing, chronic type. In coming to the proper decision, a careful history, a study of the specific gravity of the urine, and a red blood cell count are the most useful aids.

2. As in the chronic form, there are five syndromes to deal with in acute nephritis. These syndromes are discussed.

3. The four courses that acute nephritis may take are discussed, and the average recovery age is set at six weeks in the acute phase. A latent period may follow in which the patient may feel well. Upon a more careful examination of the urine, however, one may find evidence of an inflammatory lesion in the kidney.

4. The intensity of the initial stage of acute nephritis has little or no bearing on the ultimate outcome of the patient, but the duration of the disease which precipitates the acute nephritis often has an effect on the ultimate outcome of the renal lesion.

5. Difficulty may arise in differentiating the latent period from the chronic state, but as a general rule, after a two-year period, the disease may be classed as chronic.

6. The tests that are particularly helpful in determining the degree of activity of the lesion in the kidney are the dilution-concentration test of Volhard, the blood urea clearance test, the determination of the erythrocyte count, the phenolsulfonphthalein test, and the Addis count.

7. Treatment may be divided into two periods: (1) The treatment of the early, stormy phase of the disease. (2) The treatment of the later, milder stage.

8. Three chief dangers must be combatted in the first phase: (1) The danger of renal insufficiency followed by genuine uremia. (2) Convulsions which may cause death. (3) Heart failure which may occur with or without hypertension.

9. In milder forms of the disease the patient should be kept at complete rest until the lesion in the kidney has healed, and the diet should be regulated and attention given to the protein, the salt, and the fluid intake.

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Symptoms referred to the urinary tract are exceedingly common in the patients of the general practitioner. The author has reviewed briefly their significance.

Urinary Symptoms in General Practice

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One of the most frequent gynecologic complaints encountered in general practice is that of urinary distress. It is often difficult to determine whether the complaint is actually due to a disorder of the urinary tract, or whether it springs from other causes which may be genital in character. This difficulty in differentiation can be understood, since embryologically and anatomically the reproductive and urinary systems are allied, hence, the term genito-urinary system.

Medical students know well the necessity for inquiring about frequency, urgency, dysuria, nocturia, hematuria and pyuria. They have been told this often enough, but unfortunately, too few have been told, or if told, remember the significance of these symptoms. Many of the symptoms, if tracked down through the history, will give an immediate clue to the pathology.

Contrary to the usual conception, the majority of symptoms such as frequency, dysuria, pain in the bladder, urgency, incontinence, retention and nocturia may occur with a normal urine. Hence, the finding of a normal urine does not eliminate and should not conclude the search for pathology.

Pain in the bladder and urethra is a symptom of urinary lesions which may be inflammatory in nature as cystitis, urethritis, calculus, or noninflammatory as new growths (papilloma or urethral caruncle) and vesico-vaginal fistula. Frequent and painful micturition may be a symptom of pelvic disorders occurring outside of the bladder. Thus undue pressure or traction on the bladder caused by pregnancy in the first three months before the uterus rises out of the pelvis, tumors of the uterus or ovaries, cysts, uterine displacements, pelvic inflammatory disease, as well as a relaxation of the perineum which permits the base of the bladder to sag may cause pain. In any of these conditions, the urine may be normal.

Frequency is a common symptom of pelvic disorders, either of the bladder or of the structures close to it. Frequency, without burning or discomfort of any sort, implies a disproportion between the quantity of urine and the size of the bladder. The quantity of the urine may have been increased by the intake of large amounts of fluid within a short period of time; as is noted among beer drinkers who must void frequently after imbibing 5 to 15 bottles of beer within two or three hours are constantly seeking a refuge. Many people who only drink coffee on occasion state that it acts as a diuretic, which is due to the action of the caffeine. Diabetes insipidus is a pathologic condition characterized by the output of a large quantity of low concentration urine.

Frequency may occur because of a large cystocele with chronic cystitis. Under these circumstances several ounces of urine remain in the bladder. In a short while it fills again and creates the desire to urinate. In these cases, the residual urine often has an ammoniacal odor. It is the infection, or cystitis, which accounts for the irritation producing the desire to void and often the pain. Any inflammatory process in the pelvis or of the bladder, whether bacterial or traumatic in nature, may produce a frequency.

The frequent urination and discomfort incident to the relaxation of the pelvic floor is relieved when the patient lies down or when the displaced organs are supported with the aid of a pessary.

Urgency is a complaint that is met quite frequently in all types of practice, and merely represents an unfulfilled desire to urinate. It falls in the same category of desire as that of the worker in an ammunition plant "dying for a cigarette," or of the bored clerk "dying for a coke." When most of the people with this complaint void, they pass a varying amount of normal urine. Urgency, per se, is a product of civilization that dictates where one must void. It is difficult to conceive of the Eskimo or the bush native, who responds to nature's call when and where he is, suffering from urgency.

Burning during micturition must be analyzed as to time to aid in establishing a diagnosis. Discomfort in the bladder area, before voiding, suggests that the

pathology lies in the urinary tract. Pain or discomfort that begins as the urine is passed and ceases when the constrictor muscle closses suggests disease in the urethra. This may be urethritis from any cause, a urethral caruncle, or perhaps an irritation of the lower portion of the urethra due to irritating vaginal discharges or trauma. Pain in the bladder area, after urination, which gradually decreases or fades until after the next passage of urine suggests a bladder stone or papilloma which irritates the bladder walls as they come in contact with tumor or stone. Cystitis may cause pain when the walls of the bladder come together after micturition and disappears as the urine accumulates and separates them.

Incontinence, or the inability to retain the urine, may be normal if the bladder has become overly full, and the urine dribbles out on laughing, straining, coughing or sneezing. Pathologic incontinence usually occurs, (1) in women who have born children and have had injury to the sphincter muscle; (2) in women who have a vesico-vaginal fistula following either prolonged labor or radiation therapy. Urinary incontinence due to childbirth does not appear at once, but only after months or years. It is first noted as a dribbling after coughing, sneezing, or any act which increases the intra-abdominal pressure, and then as age impairs the muscle tone the dribbling occurs on the slightest exertion.

The diagnosis may be made by putting the patient on the table with a full bladder and asking her to cough—a spurt of urine confirms the diagnosis. If none is forthcoming, a careful search should be made for a fistula or aberrant urethral opening. The treatment is surgical, although occasionally dilatation with a large sound may irritate the muscle sufficiently to increase its tone.

Retention of Urine. Eliminating disease of the central nervous system as a cause of retention, this symptom may be due to (1) a spasm of the sphincter muscle as a result of (a) a concentrated urine following any pelvic abdominal operation, (b) manipulation or suturing close to the bladder, or (c) trauma inflicted by the infant's head in childbirth; (2) obstruction (a) by an acutely retroflexed fixed pregnant uterus, (b) by a stone or pedunculated tumor of the bladder in which case the patient may begin to void and then urination suddenly ceases with the production of severe pain; (3) rarely, to a large uterine fibroid which produces distortion of the urethra with obstruction. If retention occurs, catheterization with a firm rubber catheter is indicated, since glass or metal may injure or perforate the urethra without reaching the bladder. A pregnant uterus may be raised by means of a vaginal pessary, and as soon as the uterus grows out of the pelvis, the patient will be relieved.

Hematuria. When a patient states that blood has been noticed in the urine, it merely means that the urine was tinted red. This redness may be the result of bleeding along the urinary tract, or it may mean the bleeding arose along the uterine or vaginal tract, and was washed out with the urine. An occasional cause of a red tinge in the urine may be anthocyaninuria, which is caused by an abnormal pigment—anthocyanin—found in young beets, and which may be distinguished from hematuria by the fact that it is pink in acid and yellow in alkaline solutions. A catheterized specimen is of the utmost importance in determining the origin of the bleeding, and cystoscopy may reveal the exact source.

Urethral Caruncle. This is a condition that can readily be recognized if it is looked for. The visual aspect of most pelvic examinations consists of peering through a speculum. Incidentally, I prefer a daylight bulb with a head mirror such as ophthalmologists use, because it is always constant in color and intensity. A caruncle is most frequently found on the posterior wall of the urethra. It is a polypoid growth, usually single, but occasionally multiple, quite friable and bleeds readily. It occurs most frequently in elderly women with rectoceles and cystoceles, but is occasionally found in young women as a residuum of gonorrhea or chronic bladder infections.

The two confusing conditions which must be differentiated from the caruncle are malignancy, which appears as an indurated, hard tumor, the caruncle being soft, and a prolapse of the urethral mucosa. The caruncle, as already mentioned, almost always occupies the posterior wall while prolapsed mucosa forms a doughnut-shaped, red, edematous, mass with a tiny urethral opening in the center.

The chief symptoms of a urethral caruncle are painful, often excruciatingly painful, urination, a blood tinged discharge, and occasionally painful intercourse.

The treatment of the caruncle is cauterization, care being taken to remove the base and some of the surrounding mucous membrane in order to prevent recurrence which may occur when the caruncle is twisted off. This may be done with local infiltration of 1 or 2 per cent procaine.

Suburethral Abscess. This may be either acute or chronic in character. In the acute form, it protrudes from the anterior vaginal wall into the vaginal introitus. It is red and painful. In the chronic form, it is a walled-off sac which flares up from time to time and under conservative treatment will often disappear. In the acute form, hot sitz baths may effect a

cure, but occasionally incision and drainage may be required. The permanent cure consists of excision of the sac with closure of the urethral connection.

Cystitis may be chemical, traumatic or bacterial in origin, but chiefly it is bacterial. It may occur not only from a diseased kidney, ureter or urethra, but also by contiguity from an infected uterine cervix, tubes, ovary or peritoneum.

In acute cystitis, there may be frequency, dysuria, pyuria, bacteruria and hematuria. The frequency forces the patient to void every 15 minutes and the pain is excruciating. After one to two weeks, the condition becomes more endurable with occasional acute exacerbations. Fever is rarely present with acute or chronic cystitis; an elevation of temperature above 100.2° should lead one to suspect the upper, rather than the lower, urinery tract. The diagnosis is not too difficult. The treatment begins in locating the cause, which in some cases lies in the cervix and the cystitis will not clear up until the underlying cervicitis is cured, a point readily understood when one thinks of both the physical proximity and the lymphatic communication. Cystoscopy is indicated with positive urinary findings.

The treatment consists of bed rest, the intake of three to four quarts of fluid, alkalinization, sulfadiazine in proper dosage of 40 to 60 grains daily in divided doses, and when the acute symptoms subside, 30 grains daily. Sulfadiazine works well in either acid or alkaline medium, but the alkaline medium is preferred to prevent the deposition of crystals. Hyoscyamus, in doses of 15 drops every four hours, relieves the pain. If possible, local treatment and instillations should be avoided in the acute stage since they only serve to give temporary relief while forcing the infection deeper.

After the acute stage, 2 to 10 per cent of a mild silver protein or 1 to 2 per cent of a strong silver protein is used. The bladder should be emptied first, and then after the instillation may be irrigated with a warm sterile normal saline solution. Hot douches may be useful in increasing the circulation and bringing relief. As a general rule, the bladder should be irrigated only to remove clots or debris, or during a cystoscopic examination.

Pruritis Vulvae. While it may be due to actual organic disease, pruritis vulvae is occasionally due to uncleanliness where smegma has accumulated or the urine has become concentrated. This type of pruritis is irregular in appearance being present mainly in hot weather when much fluid is lost through perspiration. It may be more severe if there is pus, albumen or sugar (diabetic or otherwise) present in the urine. Pruritis is accompanied by redness, swelling and chapping of the skin of the inner aspects of the thighs due to friction, and by signs of irritation of the skin and mucous membrane of the labia.

Treatment, of course, is to increase the fluid intake and thus dilute the urine and to advocate cleanliness and the use of shedding talcum powders or ointments.

Collection of Urine. A voided specimen of urine is suspect unless it is negative. If it contains albumen, pus or blood these may be misleading artefacts due to contamination from the vagina. Therefore, it is necessary to either catheterize or collect urine in such a manner as to avoid these contaminants. One method is to wipe off the mouth of the urethra and the labia and to hold the collecting bottle close to the urethral orifice. Another method is to wipe off the parts and then hold the bulb end of a glass irrigating syringe against the urethral opening.

Ordinarily, a freshly passed specimen is acid in character. Alkalinity of a recently obtained specimen indicates urinary stagnation and ammoniacal decomposition, as found in a cystocele or in the undue ingestion of alkalies.

An offensive odor, similar to that of decaying fish, is present in chronic urinary infections associated with a bacteriuria. A fecal odor suggests a communication between the intestinal and urinary tracts. An odor of acetone may point to the pernicious vomiting of pregnancy, ectopic pregnancy, continued fever with acidosis or diabetes mellitus.

CONCLUSION

A few of the more common urologic findings encountered in a general or gynecologic practice have been discussed, as well as the symptoms produced. The most important steps in making a diagnosis are—the history, the urine and then the search for disease. The treatment of some conditions has been enumerated. In other circumstances, the case is referred to a surgeon or urologist as may be indicated, but the satisfaction of having made a good diagnosis is well worth the additional time spent.

A large number of general practitioners make a diagnosis of urinary tract disease on a voided specimen. A catheterized specimen or one collected by one of the two methods described is essential if the voided specimen is positive. Distressing urinary symptoms may be present with a negative urine.

The author presents the interesting concept of producing passive immunization in the unborn child by stimulating maternal immunity.

Prenatal Immunization with Special Reference to Pertussis*

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Medical observers have long noted the high degree of immunity possessed by newborn infants to measles, scarlet fever, poliomyelitis, and to a lesser degree, diphtheria. Conversely, it has long been known that these same newborn are particularly susceptible to certain infections—notably those of the pyogenic, colon and pertussis organisms. Between these two extremes we find a transient immunity to chicken pox, vaccinia and pneumococcic infections.

Further investigations have revealed that this neonatal immunity is apparently dependent upon four different factors. First of these is the transplacental transmission of the antigen from the mother with the resultant active immunization of the fetus. More commonly we meet the second possibility, namely, a passive intra-uterine immunity resulting from the transmission of the antibodies themselves from the mother to the fetus. Of lesser importance is the possibility of the transmission of such antibodies through the colostrum or the breast milk, and, finally, the unique immunologic features of the young and rapidly growing infant—which seem to include both certain special tissue immunities and an inadequate antibody response that is not generally overcome for the first six months or so of life.

From the viewpoint of the practicing physician, our greatest concern is the application of this knowledge to a reduction of morbidity and mortality in the young infant.

In this regard it is of present interest to note that the percentage of both the adult population and newborn infants showing diphtheria protection as manifested by negative Schick tests has been steadily decreasing as the number of actively immunized infants and children has increased. If we are to overcome the gap presented by this period of susceptibility, we must Schick test all pregnant women in the latter part of their pregnancies and if they are found to be Schick negative stimulate their antibody formation with an injection of toxoid with a resultant increase in the antibodies transmitted to their infants.

Similarly, if tetanus be especially prevalent in the community, an injection of tetanus toxoid to the mother in the third trimester of her pregnancy will confer an increased immunity upon her baby.

Our main problem, however, is that of pertussis. It is well known that this disease has its greatest mortality in the early months of life although few realize that nearly one-half of the whooping cough deaths occur in infants under five months of age.

Studies of the immunity of both the mother and the newborn have been conducted by many workers using such various indices as the opsonocytophagic reaction, mouse protection tests, agglutination tests, the Felton-Flosdorf agglutinogen skin test and the Strean toxin skin test. Although differing somewhat in percentages, the general agreement is that the immunity given a newborn infant by a mother who has had pertussis in her childhood is not sufficient to protect that infant during the early months of its life, but that if the same mother is given a course of whooping cough vaccine injections during the last trimester of her pregnancy, her infant will be protected, whether or not the titer of the antibodies is appreciably raised.

During the past year at the Hahnemann Medical College and Hospital of Philadelphia we have been experimenting with this method of prenatal immunization and with the efficacy of the Strean toxin skin test as a guide of immunity. Our present incomplete results suggest that less than half of the mothers are immune, and that nearly one-third of the infants born to both the naturally immune and the nonimmune mothers are susceptible. If, however, the nonimmune mothers are given a course of vaccine injections as suggested above, the percentage of their infants found to be immune is considerably greater. Inasmuch as

* Presented as part of a symposium on "Immunization and Treatment Procedures in Infectious Diseases" at the Postgraduate Institute of the Philadelphia County Medical Society, April 15, 1947.

other recent work seems to suggest that any test based upon the amount of antibody present may prove to be only a partial gauge of immunity, it is felt that in the future the Strean test should be further compared with such other tests as the agglutinogen skin test which seems to show relatively higher percentages of immune reactions in vaccinated individuals.

In any event, it seems definite that the administration of vaccine to the mother will increase the immunity of the newborn to pertussis, and that the diphtheria and tetanus toxoids may be similarly advisedly employed.

An interesting sidelight is that inasmuch as the injection of a strong antigen (such as the diphtheria-pertussis vaccine) seems to prevent the simultaneous action of a relatively weak antigen (such as that of the Rh factor) the use of such a vaccine in the *first* third of the pregnancy in a case in which all evidence points to an Rh incompatibility, may well result in the inhibition of the formation of the dreaded anti-Rh antibodies.

It must always be remembered, however, that any immunity obtained for the infant by stimulating the mother's antibody formation is at best a temporary one and must be followed by active immunization of the infant himself at the appropriate time.

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MEDICINE IN THE NEWS - - -

Newspapers, newsmagazines and the lay press in general have discovered or developed an intense interest in medicine among their readers. To feed this interest the reporters and writers cover medical conventions and read extensively in the medical journals of this and foreign countries. Because of their wide and energetic coverage and their interest in the more spectacular aspects of medicine, it happens more and more often that a patient will ask his physician for some new drug or treatment before the physician may have had any professional information on the subject or even be aware of its existence.

In this new department we shall briefly describe discoveries and new developments which have or may soon be publicized in the optimistic terms of the lay press. We shall endeavor to give the physician reliable information and point out the limitations as well as the rose-colored possibilities in order that he may keep abreast of the latest developments in medicine and be prepared to meet the inquiries of his patients.

PYRAHEXYL

Recently the public's attention has been directed to studies on the use of an euphoriant drug in depressive mental states, under the eye-catching term "happiness pills."[1] The studies were made and reported by G. Tayleur Stockings in the *British Medical Journal* of June 28, 1947.

The drug is reported as pyrahexyl, known also in America as synhexyl and parahexyl. This is a synthetic drug but it closely resembles in its action cannabis, mariahuana, or hashish derived from the resin of hemp and, in fact, is very closely related to the tetrahydrocannabinols, which are probably the active principles of the red oil of hemp. It was the investigation of these red oils, in an attempt to isolate the active principle of hemp, which led to the formation of the tetrahydrocannabinols and the synthesis of synhexyl and related compounds.[2]

The pharmacologic properties of the drug are like those of cannabis but are said to differ qualitatively.

[1] "Time" Magazine, July 28, 1947.

[2] "Harvey Lectures," 37:168, 1941.

According to Stockings, the drug has a specific action on the higher centers, particularly on the thalamus and its cortical pathways.

Following a latent period there is an abrupt onset of mild intoxication, sometimes with temporary anxiety, followed by exhilaration and euphoria, relief from tension and anxiety and, later, apathy and contentment. Larger doses may cause flight of ideas and pressure of activity. Hallucinatory phenomena do not occur but visual illusions may with larger doses. There are few and slight motor changes (restlessness and hyperreflexia) but ataxia only with the large doses. There are no true sensory analgesic effects and taste and hearing may become more acute. Vegetative effects such as tachycardia, dry mouth and mydriasis are slight. The effect is intermittent, coming in waves. The toxic effects are those of acute cannabis poisoning.

Because of evidence linking neurotic depression, anxiety states and similar disorders to the thalamus, and the possibility that they are not entirely psychogenic in origin but possibly the result of a metabolic disorder of the thalamic-hyothalamic mechanisms, Stockings studied the effect of pyrahexyl. Therapeutic trials were made in some fifty patients with the above disorders. Response to the drug was similar to that in normal subjects but the dose required was considerably larger, 5–15 mg. in normal subjects and 60–90 mg. in patients. Thirty-six were considered to show definite improvement. Mild untoward effects, tachycardia, slight dizziness, loss of concentration, drowsiness, and mild impairment of intellectual performance were noted. No ill effects on complicating diseases such as pulmonary tuberculosis, cardiovascular disease and thyrotoxicosis were observed.

The effect is not permanent and lasts only during the period of administration. Hence, the treatment is only palliative. Stockings considers it non-habit forming in the sense of opium or cocaine groups but the liability to addiction has not yet been completely determined. As yet no other clinical trials have been reported and it is believed to be unavailable for general use in this country.

TREATMENT OF NEUROSES WITH CO_2

The basis for recent publicity and lay interest in this form of treatment is an article on the subject by Dr. L. J. Meduna, entitled "Pharmaco-Dynamic Treatment of Psychoneuroses (A Preliminary Report)." This paper appeared in *Diseases of the Nervous System,* February 1947. It had not previously nor has it since been presented at a medical meeting.

Dr. Meduna is Associate Professor of Psychiatry, University of Illinois College of Medicine, and the work is from the Department of Psychiatry of that college and the Illinois Neuropsychiatric Institute, Chicago, Illinois. The investigation was aided by grants from the Josiah Macy, Jr. Foundation and the Rockefeller Foundation.

The treatment is based on the hypothesis that the psychoneuroses, in contrast to the psychoses, are the result of disturbances of the lower structures of the brain and hence possibly susceptible to substances or procedures which affect principally the latter. Carbon dioxide and oxygen mixtures, 20 per cent CO_2–80 per cent O_2, and 30 per cent CO_2–70 per cent O_2, were selected as the agent on the basis of previous work done by others.

The treatment procedure consists of a number of inhalations, 18 to 20 or more, and 40 to 100 or more of such treatments are given. There may be loss of consciousness and the reaction includes subcortical excitation, cortical inhibition (narcosis), psychomotor and psychosensory excitation (emotional discharges), and extrapyramidal and other motor phenomena, appearing successively. According to the author, improvement is manifested by (1) simple diminution and loss of symptoms, (2) direct abreaction of pathogenic emotions (reliving experiences), (3) indirect abreaction, the discharge of emotion by indirect means (symbolic dreams), and (4) spontaneous analysis and readjustment to a more normal personality.

Contraindication originally listed include active tuberculosis, organic heart disease and hypertension, and to those the author has since added hyperthyroidism and persistent thymus (personal communication).

Dr. Meduna states that the treatment is of no avail in the obsessive and compulsive neuroses and is without permanent effect in the so-called neurasthenic syndromes and hypochondriac neuroses.

Published reports from other sources confirming, modifying, or extending these observations have not been made and the procedure can be considered in the stage of trial at present.

The nature of gastroscopy, the principles of the technic, and the uses of, as well as the limitations of, this procedure are described in this article.

The Clinical Aspects of Gastroscopy*

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WASHINGTON, D. C.

To me, the history of many of our more commonly used methods of diagnosis is intensely interesting and illuminating from the point of view of the length of time that elapses between the time the particular procedure was introduced and the time that it became generally used by the medical profession. Almost without exception, a comparatively tremendous lapse of time intervenes. For instance, the cystoscope, in practically its present form, was first perfected as far back as 1871. Yet, when I was in medical school, it was still considered to be a manipulation that was only to be undertaken in exceptional situations and carried with it serious hazards. For years the sphygmomonometer was held almost in disrepute. Even roentgenology lay somewhat in the backwash for many years before it finally was made part of every doctor's approach to a diagnostic problem. When you consider all these instances together, the reason for the lag becomes rather clear. When a new method of diagnosis is first introduced we greet it with enthusiasm and hope that it is the thing that we have been looking for these many years—that it is going to give us all the answers. We may try it extensively and then become disappointed because we find that it has limitations. Perhaps, because we do not realize the limitations, we fall into a number of errors. Our natural inclination in our disappointment is to discard the method as being unreliable. In the early days of x-ray it was thought that an anterior-posterior chest plate would tell everything that was wrong with a person's chest, and that if it were negative there was absolutely no disease process present in that region. Then it was found that there were a number of conditions that either couldn't be demonstrated or needed a special technic for their detection. It took a long time to overcome the first antipathy and to assume a correct attitude towards this most valuable means of diagnosis. I suppose all of us at some time or another have come in contact with a person who suddenly drops dead a short time after having had an electrocardiogram taken and his heart pronounced sound. Even the most commonly used precision diagnostic instrument, the sphygmomonometer, fell into disrepute because we found that the original dictum of "your age plus a hundred" was not a correct estimation of the average blood pressure. And so one could go on, almost endlessly, citing such instances. The main lesson to be gained is to realize that every diagnostic instrument or test has its limitations, both in connection with the instrument or the technic, and with the human being that operates it. We still have to use all our faculties in arriving at an answer, and employ every means at hand to aid them.

As far back as 1868, Kussmaul in Vienna, designed a gastroscope which was primarily an open tube illuminated by an ingenious alcohol lamp at the eyepiece end. The best that could be said about this attempt was that he was able to glimpse the mucosa that lined a sword swallower's stomach. Crude as it was it marked a distinct landmark in peroral endoscopy. Mikulicz, in 1882, produced a rigid metal tube, using the optical principle of the cystoscope which had been perfected ten years previously. This was in many ways a practical instrument inasmuch as he was able to examine the stomachs of a great many different individuals, both patients with disease and professional sword swallowers. However, as might be expected, he had a certain number of serious accidents, and the procedure was not popular. From then on, however, the idea of looking into the stomach captured the fancy of a great many workers in Germany and Austria, and an incredible number of different instruments were designed and tested, each one trying to overcome the many anatomic difficulties that were naturally present. There isn't an idea along this line that has not already been tried. In 1907, Chevalier Jackson perfected an open tube gastroscope which was nothing more than an elongated esophagoscope,

* This paper was read on February 11 as part of the presentation of the Gastrointestinal Section of the Intensive Post Graduate Courses given at George Washington University Medical School, Washington, D. C., during the Spring of 1947.

which he uses today for the purpose. It is of no use from a diagnostic point of view and the number of foreign bodies that need to be extracted from the stomach are few and far between. In 1911 Elsner came out with a straight, rigid, closed tube gastroscope, whose principal distinction from those which preceded it was that it had a flexible rubber tip which materially aided in guiding the end of the instrument around the angulation of the esophagus at the cardiac end. This was a diagnostic instrument pure and simple and remained the standard until the perfection of the flexible instrument in 1932. Shortly after the last war, Rudolph Schindler in Vienna became interested in the subject of gastroscopy in connection with the many cases of malnutrition resulting from starvation during the war. He used the Elsner instrument, was decidedly dissatisfied with it and started collaborating with an optical instrument maker in Jena. After a great many attempts, one being an instrument that was flexible throughout its entire length, they finally perfected their instrument in its present form. Schindler was brought to the University of Chicago, in 1934, to introduce his methods and instrument into this country. Shortly thereafter he began collaborating with the Cameron Company in Chicago and an improved instrument was brought out, of American manufacture. Then as a further improvement the present so-called omniangle scope was perfected, which is a great deal better than the old ones.

The instrument itself is probably well known to most doctors and needs little demonstration. It consists of a rubber finger tip, a small but extremely powerful light which operates on 12 volts of current from a rheostat, the glass fronted objective, the rubber covered flexible portion which is 43 cm. in length, the rigid part, 34 cm. long, and the conventional ocular. The flexible portion contains 48 short focal length lenses, each mounted in a short brass collar and all held together by a spiral spring. This in turn is covered by two rubber sleeves, which provides a channel through which the air that inflates the stomach can be pumped in by means of a double hand bulb. The handle contains the switch which is connected to the light by means of two wires that run around the spiral spring. The handle also marked the position of the ocular which is most important for methods of orientation. In the original German instrument there was only one wire inside and the outside of the instrument acted as the other conductor. This was unsatisfactory because it made it a little dangerous to use with a rheostat, and dry cells were employed as a source of current. In this particular instrument there is a small mirror at the objective, instead of a prism, the angle of which can be changed by means of a small solenoid operated from a small button at the base of the handle. Current for lighting the lamp and operating the solenoid is obtained from a simple rheostat designed to deliver up to 25 volts. However, for examination purposes 12 volts is sufficient.

The original German instruments were of two types, which differed only in the angle of vision obtained at the objective; one subtending an angle of 45°, the other 85°. The latter provided a greater field of vision, but the former provided greater magnification. I have used both extensively, and always preferred the 45° instrument.

In as much as there are comparatively few contraindications and dangers to the routine use of this instrument, practically all persons who have worked in this field feel that it should be employed routinely in all disorders of the upper gastrointestinal tract. Of course obstructions at the cardia and in the esophagus, particularly neoplasms, contraindicate its use. So does an obvious aneurysm of the aorta because of the danger of producing premature rupture, and also because of the angulation of the esophagus produced by it. Corrosive or phlegmonous gastritis is a real danger because they produce a friable condition of the gastric wall, with the resultant danger from perforation. If, for any reason, esophageal varices are thought to be present and have bled, particularly in association with liver disease, the patient should be thoroughly studied by other means before the passage of this instrument is attempted. Certain other conditions require the services of a skilled operator and gastroscopy should not be attempted by anyone without considerable experience. These conditions are: angina pectoris, dyspnea, orthopnea, severe kyphosis of the spine, actual organic cardiospasm, esophageal diverticulae, and active severe psychoses.

TECHNIC OF THE EXAMINATION

The preparation of the patient for this examination presents no particular difficulties. He is told to partake of a light meal the evening before and to refrain entirely from consuming any breakfast, although he may drink water if he is thirsty. Do not allow him to brush his teeth as the swallowed tooth paste or powder may obscure the view. He reports to the place of examination at the appointed time, which should be as early in the morning as practical. He is given an injection consisting of codein phosphate grains one half and atropin sulfate grains 1/150, and then sits quietly for one-half to three quarters of an hour. He is now ready for the regional anesthesia of his hypopharynx. Pontocaine is the drug of choice because of its almost

total lack of side reactions, and is used in two per cent dilution. Each endoscopist that I have observed uses a slightly different technic. I first have the patient gargle a dropper full of pontocaine and then spit out as much as possible, and after a couple of minutes gargle another. I then pass a short perforated rubber tube which goes only as far as the beginning of the esophagus and squirt in 5 cc. of 2 per cent pontocaine with as much pressure as I can, using a metal tipped syringe. This is usually sufficient but if the anesthesia does not seem adequate I inject another 5 cc. Some gastroscopists shorten this procedure by using a long-nozzled atomizer and spraying as far down the hypopharynx as possible. This procedure effects an adequate anesthesia but after trying this method rather extensively, a number of patients experienced short lived, but alarming, circulatory collapse which I attributed to absorption of the drug through the bronchial mucosa or the alveoli themselves. Anyway, I discarded the method and no more trouble in this direction was experienced.

Schindler advocates completely emptying the stomach before proceeding any farther with the examination. This he accomplishes with a large soft Ewald type of tube and gravity, the patient being so placed on a specially constructed table as to have his head lower than his abdomen. I have given this up unless I am dealing with a patient in whom I suspect a gastric retention. The passage of the tube upsets the patient unduly and I have found that if he is properly prepared there is practically no fluid in his stomach. So when satisfactory anesthesia has been effected the patient is placed in the proper position on the examining table, on his left side with his left arm under him and the forearm flexed at 90°. The assistant holds his head in the normal position. The patient opens his mouth and the tip of the instrument is then introduced into the pharynx and the finger of the operator guides it down the bend to the beginning of the esophagus, past the periform sinuses. From then on gentle pressure eases the 'scope down the length of the esophagus, past the angulation at the cardiac end where it usually hesitates for a moment, and finally into the stomach to its farthest depth. The operator switches on the light and gently pumps in a bulb full of air or so and takes a look. If everything has gone well, and the handle of the instrument points toward eleven o'clock, he will be looking directly at the pylorus. This is the first and really only landmark, for if you don't find this there is no way to tell exactly where you are. From then on it is a matter of rotating the instrument, pulling it out a short distance, and rotating again until the entire inside of the organ has been examined and you are at the cardia. When you are satisfied that you have seen everything in which you are interested, the 'scope is gently withdrawn and the patient told to sit up and belch the air. As soon as he accomplishes this he feels perfectly all right and is usually ready to go home without more ado.

It must be emphasized here that the psychological handling of the patient is one of the most important aspects of the entire examination. This must be realized particularly by the physician who refers a patient for this type of examination. There seems to be a great tendency to joke with the patient and allude to the swallowing of swords or other such gruesome analogies. This sort of thing is on a par with laughing when a person slips and falls, fracturing the coccyx. Instead, the referring doctor should explain exactly what the procedure is and not try to minimize it. He can liken it to the passing of the Ewald stomach tube. In fact when this tube was first introduced, about the turn of the century, the technic for passing it was more complicated than that of passing the gastroscope. He can tell the patient that following the examination he will feel perfectly all right except for the possibility of a slight sore throat which may persist for 24 hours. I have found also a tendency on the part of some doctors referring cases to use the examination as a sort of punishment or a peculiar method of psychotherapy. In other words, to teach the patient a good lesson and let him know when there was really something wrong with him. Needless to say I am not at all in favor of this. By far the greatest difficulty encountered by the gastroscopist is apprehension on the patient's part, and anything that can be done to allay this state of mind will further ease the performance of the examination. In sincerity I can say that I have had practically no patients who have refused to be examined a second time and I cannot recall a single instance in which a patient advised, or influenced, another patient not to be examined, even though a great deal of my work has been done in clinics and hospitals where patients have ample opportunity to exchange viewpoints and influence others were it their wish to do so. The preliminaries and the actual examination should be carried out in an atmosphere of calm. The examiner and his assistants should work in harmony and should know exactly what the other wants without asking questions. They never should give the slightest hint of any uncertainty as to what is to be done next, and no one should get excited no matter what happens. Any feeling of indecision is immediately transmitted to the patient and produces restlessness or spasm, both of which prolong, or may even spoil, the examination. Of necessity the examination takes place in a small

room that can be darkened. Visitors should make every effort to be quiet and should reserve all questions until the examination is over. Particularly, they should refrain from any alarming remarks if they themselves look down the gastroscope and see something that they don't understand. Visitors should also control themselves and not try to assist in holding a patient or calm him should he become a little disturbed. The examiner and his assistant will have the situation in hand, and will have experienced many times in the past any difficulty that may arise.

When gastroscopy is part of a routine check-up and there is nothing wrong with the patient that requires other procedures, the examination can be done as an office procedure and the patient can go home afterwards. There are no bad after-effects to be anticipated. In cases involving a particularly apprehensive individual, or one in a highly tense state, it may be well to hospitalize him the night before and give him a dose of morphine or pantopon before he retires.

DIFFICULTIES AND LIMITATIONS

As I have stated, gastroscopy should be used routinely in the diagnosis of diseases of the upper gastrointestinal tract. However, it does not supersede any of the other methods of diagnosis and it is a great mistake to think that it does. Like any other means of diagnosis it has its limitations, and these should be thoroughly understood by the physician who is going to use this aid in arriving at the answer to a difficult problem. The mere fact that a gastroscopist sees nearly the entire inside of the stomach does not mean that he can know every single solitary thing about it. It should be used in conjunction with the x-ray and not instead of it. There are certain parts of the stomach that cannot be seen, the most important being the greater part of the lesser curvature of the antrum. It is difficult, without a diagram, to explain why this is true, except to say that the inscisura angularis gets in the way of the field of vision. Frequently, external manipulation of the stomach wall can overcome this shortcoming, but not always in a completely satisfactory fashion. In addition there is a portion of the dependent part of the posterior wall which lies just below the tip of the instrument that cannot be seen, as well as a small part of the fornix. Luckily these two parts of the stomach are relatively free of pathologic lesions. It must be remembered that you see only the mucosal surfaces, and not the structures that lie underneath. Lesions involving the muscularis and the serosa of course cannot be seen, but their presence frequently can be detected by indirect methods. The fact that the operator is able to see a lesion, and describe its appearance minutely, does not necessarily mean that he can always tell exactly what it is. Even in such easily accessible lesions as those that occur on the skin, the dermatologist cannot always arrive at a correct diagnosis, even though in addition to being able to see the lesion, he is able to feel, smell and make a biopsy of it. So, as you can readily see, we cannot make a diagnosis by any one means exclusively. We must use every method at our disposal, and even then it is a difficult proposition. From a purely selfish point of view this is probably a good thing because otherwise there would be no place in medicine for an internist, his present function would be taken over by the laboratory or the doctor doing special types of examination.

It should be noted here that it is impossible to see the inside of the esophagus with the gastroscope or to see beyond the pylorus into the duodenum. The reason is quite clear when you examine the structure of the gastroscope. In the case of the esophagus its walls closely enclose the window of the objective and do not permit light which comes from below to enter. The same thing would apply in the stomach were it not for the fact that one can distend its walls by inflating with air. When viewing the pyloric orifice the objective lies about 7 cm. away from it. The opening is not large enough, nor is the source of light strong enough, to permit a view beyond. It is impossible to get the tip of the gastroscope inside the duodenum, and if it were, then the same difficulty would be met as occurs in the esophagus. Many ideas to overcome this difficulty have been suggested but so far none has been practical. It is a fact that with sufficient light an image can be transmitted around a bent rod of lucite, and it has been hoped that this principle could be incorporated into an attachment that would permit of a view of the duodenum, but no success has so far been reported.

Even though the electric light which illuminates the objective is extremely bright as measured by a light meter, the system of 48 lenses absorbs so much of it that by the time it is emitted from the eyepiece it is relatively weak. This is true even though the image that falls on the retina seems very bright. In order to see at all well the examining room must be in almost total darkness. Because of reflection, an uncoated lens loses about 10 per cent of the light that passes through it. Inasmuch as we are dealing with a system of 48 lenses it is easy to see that if each lens loses 10 per cent of its light, there is relatively very little that finally reaches the retina. The special coating that was developed during the war for lenses of binoculars, periscopes and other optical instruments greatly re-

duces this light loss and it will not be very much longer before the lenses of the gastroscope are so coated. This may aid materially in the matter of photography. It is perfectly possible to take a picture through the gastroscope using the usual color film, but unfortunately it takes a half a second or longer. Inasmuch as the stomach is in constant motion it is obvious that this is far too slow a speed. Using faster film emulsions this speed might be increased, but a satisfactory picture will not be obtained until we are able to use a speed of at least 1/50 of a second. So far this is impossible using even the fastest film obtainable.

So far the only way to represent satisfactorily in color what you see is to have an artist trained to observe through the gastroscope and paint what he sees. Then, in conjunction with the operator a satisfactory picture can finally be arrived at. This method is costly and the artist is not always available when you want him. Some years ago I was lucky enough to have a very excellent medical artist as a ward patient, and during the time she was in the hospital she worked with me a great deal, even though she was confined to a wheel chair. I obtained a number of excellent sketches from her.

POSSIBILITIES OF THE GASTROSCOPE

The question now arises as to exactly what you can expect to accomplish with a gastroscopic examination. I shall go into this matter in some detail. First, and perhaps most important, is to be able to say that the mucosa, the rugal folds, the peristaltic action and the function of the pylorus appear normal. The recognition of normalcy can be gained only after a great deal of experience, and this sort of a report is of great value in the differentiation of functional from organic disease. This is a differential diagnosis that we have to make more often than any other. Of course a report such as this is only of value in conjunction with the results of all other examinations. It is of no particular importance to recognize the pallor due to anemia, which is recognizable only when the hemoglobin has dropped below 50 per cent. An intensification of the normal orange red color in conjunction with numerous mucosal hemorrhages may occur in polycythemia vera. Varices of the stomach are rare. I have never seen such a condition though Schindler reports seeing them on several occasions. Mucosal hemorrhages are frequently seen in an otherwise normal appearing stomach. These need not necessarily be inflammatory in origin, and may happen in conjunction with a hemorrhagic disease such as purpura hemorrhagica. With the mucosal hemorrhages there may be brown pigment spots which apparently develop from the hemorrhages. Some of the hemorrhagic areas may ulcerate and erode. These hemorrhages, erosions and pigmented spots are frequently seen with gastric and duodenal ulcers, in either the active or the healing stages, and have led to speculation concerning the etiology of these two conditions. The hemorrhages may be due to stasis resulting from prolonged irritation of the vasomotor nerves; or, they may result from trauma, as they are seen mostly on the *Magen Strasse*. The digestive action of the gastric juice plays some role in transforming them into actual ulcerations.

A duodenal ulcer cannot be visualized, nor one involving the pylorus itself. When the ulceration is chronic and is near the pylorus, it is frequently noted that that structure is distorted and pulled upwards and is found either in a location where you don't expect to see it, or not seen at all. When such a condition is encountered it may be considered indirect evidence of the presence of such an ulcer. Even though pyloric ulcers cannot be seen as a rule; a pyloric carcinoma can be visualized practically every time. Also, when an active ulcer is present in these localities there is considerable antral gastritis with erosions and hemorrhages. This is characteristic of the so-called "ulcer stomach." Prepyloric ulcers are visualized, though not as easily as might be expected, probably because of the distortion that takes place after the ulcer has been present for any great length of time. Most gastric ulcers are on the lesser curvature and are easily seen unless they happen to be in the blind spot. If they are, they can be demonstrated readily by x-ray. Ulcers present a characteristic gastroscopic appearance and are easily recognizable. They stand out as round or eliptical, white or yellowish white, areas with a sharply defined, punched out, rounded edge surrounded by a red zone of inflammatory gastritis. Experience teaches one to estimate their depth and size, but there is no means of actually measuring them. Occasionally, actual bleeding from the floor of the ulcer may be seen, and frequently folds of mucosa are seen converging towards it in a stellate fashion. The surrounding mucosa may be swollen, deep red and edematous. It is possible that a penetrating ulcer which is just on the point of perforating might do so when the stomach is inflated with air, but so far such a complication has not been reported. While profuse hemorrhage is in progress gastroscopy is contraindicated for obvious reasons; the patient is too sick, the lens of the instrument would be clouded with blood. However, the procedure may be undertaken as soon as the active bleeding has ceased. It may be

pertinent to state here that as a rule, in cases of profuse hemorrhage, we wait too long before we attempt active methods of locating the source of the bleeding. It may be that even though an active ulcer is present, the actual bleeding may be coming from an erosion some distance away; or, there may be some other lesion present in the stomach, such as a benign tumor. Occasionally, in the case of an ulcer of long standing, there will be what appears to be a cicatricial deformity producing an hour-glass type of stomach and gastroscopy may be of value in determining whether this deformity is due to actual stenosis or to spasm. In my own particular experience I have never observed a stenosis of the pylorus although I have examined a great many patients with marked gastric retention.

It is easy to follow the course of healing of an ulcer. Because the ulcer niche may disappear radiographically does not necessarily mean that it is covered over with epithelium. The niche may be filled with exudate, or surrounding edema may have closed its orifice. The actual time that it takes an ulcer to heal completely is problematical. Schindler states that it takes about seven and one half weeks on the average, but I have observed several that have healed completely within two weeks. Generally speaking they heal without any visible scar formation, even large ones leaving no gastroscopic trace, although the pathologist may report a large converging scar. It may be well to note that the acute erosions heal in about 48 hours and might be likened in this proclivity to canker sores in the buccal mucosa.

TYPES OF GASTRIC LESIONS

Acute gastritis, generally speaking, is not a gastroscopic problem. The patient is usually too sick to be so examined, and in the case of corrosive or phlegmonous gastritis, it would be dangerous. The simple, acute, exogenous type was well described by William Beaumont in his many observations on his patient Alexis St. Martin. I have had practically no experience in observing this type of disease except in the case of several chronic alcoholics after acute debauches, and it is problematical whether I was looking at acute gastritis or chronic superficial gastritis. However, chronic gastritis is another problem. This diagnosis was very much in vogue prior to the extensive use of x-ray methods of diagnosis, because, radiographically the condition is not demonstrable except in its more pronounced forms. Therefore the diagnosis fell into disrepute and was not heard in most medical circles for many years. From a gastroscopic point of view it has become a well recognized disease entity. In 1923 Schindler published his "Lehrbuch und Atlas der Gastroskopie," which contained many color prints showing various forms of chronic gastritis, and was based on many observations made with the old rigid Elsner type of gastroscope. Most histologic descriptions of the normal stomach are based upon the appearance of the normal infant's mucosa, and to my knowledge no exact criteria as to what constitutes a normal adult's mucosa from a microscopic viewpoint have been established. Therefore, as Henning said, "if the term chronic gastritis were applied to that condition shown by any anatomic alteration of the gastric mucosa, then there would be no adult without chronic gastritis." With the usual wear and tear of adult life and the numerous insults that are perpetrated on the gastric mucosa, many resultant changes are found that cause variations from the appearance of an infant's stomach, but are not necessarily abnormal. What can be considered normal wear and tear and what should be considered pathologic is a great question. A classification using etiology as a basis would of course be the best way to classify the various forms of gastritis, but unfortunately very little is known about the actual cause of these various conditions. Certain observers believe that each different picture is but a stage in a single process, and have gone as far as to say that all stages can be seen in a single diseased stomach. Another very simple classification would be by the location of the diseased process; dividing it into antral gastritis and gastritis of the body of the stomach. However, in most instances the entire stomach is involved. This would make this classification unsatisfactory, even though the greater part of the pathology occurs in the body. Keith Simpson suggests the following classification: (1) Acute gastritis, which includes simple parenchymatous erosive, hemorrhagic, and erosive membraneous; (2) subacute gastritis, including simple parenchymatous and hypertrophic; and (3) chronic gastritis or atrophic gastritis. The terms acute, subacute and chronic refer not to the duration of the disease but to the histologic appearance. Schindler in 1922 introduced his classification based upon a correlation of the gastroscopic findings and the course and prognosis of the disease. It is as follows: (1) Superficial gastritis; (2) atrophic gastritis; (3) hypertrophic gastritis; and (4) gastritis of the postoperative stomach. This classification I have found to be the most satisfactory although it has its limitations. I shall now go into some detail and describe these various conditions.

Chronic superficial gastritis, generally speaking, is found in the body of the stomach and shows three characteristic signs, namely, reddening of the mucous membranes, edema and exudation. The reddening represents areas of hyperemia, is carmine red in color, patchy in distribution, and the patches vary considerably in size. In addition, certain of the rugal folds may show a reddened, nontransparent ridge. The edema is represented by a moist swollen appearance of certain areas of mucosa, and there is an increase in the highlights. The color in these particular areas may be paler than that of the surrounding mucosa. The exudation resembles in general that found in other inflamed mucous membranes, but may very easily be mistaken for swallowed saliva or retained normal secretions. Fluid mucus or actual membrane is considered pathologic only if it adheres to the surface of the mucosa. It may vary a great deal as to transparency and color. When thick and very adherent it is usually surrounded by a narrow border of deep red mucosa. All inflamed mucosal surfaces tend to bleed easily, and in this particular type the areas of bleeding are not large, are superficial, and consist of small irregular spots lying on the edematous mucosa. The inflamed mucosal surfaces are easily injured by trauma, and will bleed when touched by the tip of the instrument. Sometimes you can follow the course of the gastroscope down the posterior wall. There also may be small superficial erosions. Inasmuch as this is a relatively benign disease it has been almost impossible to obtain suitable pathologic specimens for microscopic examination. However, they show apparently extensive interstitial infiltration of the superficial layers of the mucosa between the neck of the glands and the surface epithelium, with many plasma cells, round cells and some eosinophils. The capillaries in the superficial layers of the mucosa are enlarged and in some instances actual rupture of one may be demonstrated. The actual cause of chronic superficial gastritis is not known, although many factors have been suggested. These are excessive consumption of liquors, lack of teeth, malnutrition, nicotine, salicylic acid, excessive use of alkalies, anomalies of the gastric secretion, uremia, lead poisoning, excessively hot or cold foods, certain bacteria, certain protozoa such as Giardia, focal infection, passive congestion, and various nervous factors. There are no specific signs or symptoms by which this type of gastritis can be diagnosed clinically. It usually occurs in the third decade.

The gastroscopic picture seen in chronic atrophic gastritis is extremely characteristic, the most striking feature being the thin mucosa, which may be green or grayish-green in color. There are usually well-defined patches which are slightly depressed, but also the edges may gradually merge into normal or superficially inflamed areas. Once seen it is easy to differentiate from the pale pink, nonsunken mucosa found in anemia. As the thinning of the mucosa progresses the dark blue, tree-like branches of the larger blood vessels in the submucosa begin to show through. This is the only condition in the stomach where the blood vessels are visible and is pathognomonic of this condition. The rugal folds are somewhat flattened. Complete atrophy of all the gastric mucosa is quite unusual but does happen. Large mucosal hemorrhages may occur and heal quickly. In the latter stages of this chronic atrophic gastritis there is a complete atrophy of the entire mucous membrane of the stomach. Prior to this end-result there is a very characteristic transformation of the surface epithelium into goblet cell epithelium resembling that found in the intestinal canal. The mucosal surfaces are covered with cylindrical epithelium which contains a number of goblet cells and the typical glands are replaced by those found in the intestinal tract. With the shrinking and disappearance of the glands there occurs an infiltration of round cells, plasma cells and fibroblasts, and in some instances thick layers of dense connective tissue are formed. It has been observed often enough to make it seem possible that superficial gastritis tends to develop into atrophic gastritis, and therefore the two have a common cause. Schindler feels that if untreated, superficial gastritis will eventually become atrophic. There may be some hereditary factor involved as well. Atrophic gastritis never occurs in a person who seems perfectly well in other respects. However, there are no localizing signs or symptoms, and the patient seems to be suffering from a systemic disease rather than a local disease of the stomach. The x-ray picture does not help and it is wrong to assume that you will find flattened rugal folds by this examination. Henning feels that complete atrophy is found in every case of pernicious anemia, but Schindler thinks that this is unsual and that the atrophy is usually patchy. The same picture can be found in combined cord degeneration without anemia. Faber believes that chronic gastritis is the primary factor in the etiology of pernicious anemia, and that this disease develops only in those instances in which the glands of Brunner are destroyed, and that these glands contain the intrinsic anti-anemic factor. If the glands of Brunner in the duodenum remain intact then the anemia does not develop, even with total extirpation of the stomach. Schindler states that with liver treatment, the progress of atrophic gastritis is reversed.

Chronic hypertrophic gastritis as a clinical entity differs quite markedly from the two aforementioned types of gastritis. The changes seen in the advanced form are easily recognizable, but the early changes are not nearly so easy to differentiate. The principal location is in the body of the stomach. The first gastroscopic sign is the appearance of a velvety look to the mucous membrane. It appears slightly swollen, dull, loose and spongy. The highlights are greatly diminished or completely lost, the reason being that instead of the light being reflected back by a smooth surface it is diffused by the roughened surface. These changes first appear in the valleys between the rugal folds and as the disease progresses nodules of various size appear. The creases make up the boundaries of irregular polygonal areas of different size which become irregularly elevated; sometimes the tops appear reddened. There may be varying sized hemorrhages or hemorrhagic areas. The varying degrees of development may be described by such terms as "granular," "nodular," "verrucose," and "hemorrhagic." At times the nodules may be so large as to be mistaken for polyps, although they differ from true polyps in being loose, spongy, bluish and almost transparent. When the mucosal folds themselves are affected they become irregular and subdivided by perpendicular folds which eventually may take on a worm-like appearance. Small, multiple, shallow ulcerations frequently form, and have a yellow base and reddened edges. An increase in secretion is rarely noted. Those cases showing marked hypertrophy have an interstitial infiltration throughout the entire mucous membrane. This consists of round cells, plasma cells and a few polymorphonuclears. Very little is known concerning the etiology of this condition. None of the before mentioned exogenous factors seems to have much bearing, except alcohol. The condition can produce exactly the same symptoms as peptic ulcer, and they may even be much more severe. There are no clinical features to differentiate the two conditions. The x-ray picture is unreliable, except perhaps in the very advanced forms. The disease itself never seems to heal even though the symptoms may disappear completely.

With the exception of syphilis of the stomach, granulomata have been observed rarely by means of the gastroscope, but the gastroscopist must keep their anatomic picture in mind. Anthrax, tuberculosis, actinomycosis and lymphogranulomatosis are the most important. In syphilis, perivascular gummata and an obliterating endarteritis are found in the vessels of the submucosa. Circumscribed, tumor-like elevations may be present and may lead to pyloric obstruction. With breaking down of the gummata, shallow ulcerations may arise, and may vary tremendously in size. In some cases the process is extensive and the stomach assumes a leather bottle form.

Benign tumors of the stomach are by no means rare. Some arise from the muscularis and the subserosa and lie outside the gastric cavity. They are not particularly important unless they impinge upon the stomach because of their size. The important tumors are those that arise inside the stomach and protrude into its lumen. Because of their size and location they may cause serious trouble and even obstruct the pylorus. They may bleed severely, may even degenerate and become malignant. Tumors of mesenchymal origin, such as fibromas, neurofibromas, myomas, fibromyomas, lipomas, lymphomas and hemangiomas, have been observed, and, except for the hemangiomas, are difficult to differentiate. However, they can be told from tumors that arise from the epithelium because the epithelium is not involved and stretches over them. Cauliflower papilloma are rare but because of their great tendency to become malignant should be removed as soon as they are recognized. Small benign polyps are very frequent and may be solitary or multiple. They are difficult to differentiate from pseudopolyps.

Carcinomas may be classified in two ways: according to the microscopic appearance or the macroscopic appearance. The first classification is as follows:

A. Adenocarcinoma
 1. Carcinoma cylindrocellulare
 2. Carcinoma papilliferum
 3. Adenoma malignum
B. Carcinoma alveolare solidum
 1. Colloid
 2. Scirrhous
C. Diffuse polymorphocellular carcinoma
D. Mixed forms

From a gastroscopic point of view the following macroscopic classification of Borrman is the most practical:

A. Carcinomas which are prominent, sharply defined, polypoid, with broad base and with little ulceration.

B. Extensively ulcerated carcinomas with raised margins. In these one is able to state, using the sense of touch, that the wall-like margin is really the limit of the carcinoma because the stomach wall beyond this sharp edge slopes suddenly and steeply and becomes very thin.

C. Ulcerated carcinomas, in which the steep, sudden sloping of the wall to a normal mucosa is missed and in which the infiltration of the stomach wall goes beyond the edge of the ulcer and only gradually dis-

continues. In these cases the carcinoma grows farther in the submucosa than one would suspect from macroscopic examination.

D. Diffuse carcinomas which are ulcerated but little, which do not permit their limits to be judged by the sense of touch and which infiltrate the stomach wall. This infiltration becomes gradually less toward the cardia.

This classification can be further simplified:

A. Polypoid carcinoma
B. Noninfiltrating carcinomatous ulcer
C. Infiltrative carcinomatous ulcer
D. Diffuse infiltrating carcinoma
 1. Diffuse scirrhus infiltration of the whole stomach wall
 2. Partial infiltration caused either by medullary or scirrhus carcinoma

Space does not permit a detailed description of the gastroscopic pictures seen in these various types of carcinoma. Nor is it advisable to discuss operability and prognosis at this time. However, something may be said concerning the relationship between benign ulcer and carcinoma. It has been shown that in a carcinomatous ulcer the destruction and degeneration of the carcinomatous cells can be so complete that parts of the ulcer may appear benign histologically. Schindler states that he has never seen carcinoma develop in ulcers that he has observed over a period of years. However, be that as it may, gastroscopy usually permits of the differential diagnosis between benign and malignant ulceration.

The edges of a carcinomatous ulcer are not as sharp as those of a benign ulceration. The floor is irregular and contains nodules, nodes or ridges; its color is sometimes whitish or yellowish, but more frequently is brown, brown-red, violet, gray or a dirt color. In the adjacent surface, at least in later stages, nodes are found that differ in their size and irregularity from those of hypertrophic gastritis. This type of ulcer usually lies more or less on a hill, thereby differing from a benign ulcer. An associated atrophic gastritis is very frequent. The chronic benign ulcer is generally crater-like, and in only rare instances is it shallow. The floor is whitish yellow, is very rarely brownish, though after an acute hemorrhage it may be dark red. Its edges are sharply defined and often partly undermined. In early lesions the surrounding mucosa is often normal in appearance, and later there may be marked inflammation of the surrounding mucosa but rarely of the entire stomach.

Sarcomata are rarely found in the stomach. Round and spindle cell types are very rare; lymphosarcoma is more frequent. Following an operation involving the stomach it presents an extremely interesting appearance but is more difficult to examine than one not operated on because of difficulty of orientation. Suffice it to say that a stoma never looks like a slit, but instead shortly assumes the appearance of a sphincteredorifice and with even a rhythmic opening and closing.

In conclusion let me repeat one of my previous points, namely, that the gastroscope does not answer all problems concerning the differential diagnosis of disturbances of the upper gastrointestinal tract. It has its definite limitations, but it also has unquestioned value and should be looked upon as a routine diagnostic procedure.

1834 Connecticut Ave. N.W.

WHAT'S YOUR DIAGNOSIS?

A 38-year-old white carpenter was admitted to the medical service on February 15, 1940 because of a skin disease of 17 years' duration. This rash first appeared as a scaly eruption on the legs below the knees and in the scalp. They were worse in cold weather and cleared entirely during the summer. They were mildly pruritic. A few months before he was admitted the rash spread to involve the knees, elbows, both shoulders and trunk. The scales had a silvery appearance. On the advice of his druggist the patient took Fowler's solution, several drops three times daily, for a short time without effect. He then consulted his physician who first gave him a salve, then some small gray tablets which had no effect.

About one month before entry he received the first of four intravenous injections which were thought to

contain arsenic. The first two injections had no effect. About six hours after the third injection, which was two weeks before admission, he became nauseated and vomited. Shortly after this he noted erythema of the skin of the legs and abdomen. About three days later while the erythema was still present the fourth injection was given. After this he noted swelling of the legs and spread of the erythema to cover the entire body. This was followed by desquamation. After the last intravenous injection he was given a clear liquid to take by mouth. He thought that this was Fowler's solution and he took five drops three times a day until the time of admission. He felt chilly before admission but had no shaking chills or fever. He had had a nonproductive cough for several days.

Systems review and past history revealed a three-year history of stomach trouble characterized by periodic midepigastric, dull aching pain which began about two hours after a meal and lasted for about an hour. It was invariably relieved by soda and small amounts of food. It was aggravated by onions, large amounts of meat and white beans. There was no history of jaundice, hematemesis, melena or flatulence.

The patient's mother had tuberculosis.

Physical Examination: T. 98.4, P. 100, R. 20, B.P. 115/75. He presented a remarkable appearance. The skin was exfoliating generally in white, rough, thick scaly areas. There was a diffuse bright red color over the entire body. He was very uncomfortable but did not appear to be critically ill. There was generalized edema, most marked about the eyes, almost closing them. Slight pitting was present over the ankles. The scalp was involved in the scaling process. The skin was everywhere intact and there were no breaks or infections. A generalized enlargement of lymph nodes was present. The eyes were normal. Ocular fundi showed no abnormalities. The teeth were dirty and carious. The gums were retracted. No mucous membrane lesions were seen. A few small punctate hemorrhagic areas were noted on the hard palate. Several large cervical lymph nodes were noted. The thyroid gland was not remarkable. Lungs were clear. Heart was not enlarged. Rhythm was regular. A soft systolic murmur was heard at the apex. No diastolic murmurs were heard. The abdomen was soft and no organs or masses were felt. The liver descended one to two fingersbreadth below the costal margin by percussion. Genitalia normal. Rectal sphincter tone diminished. Prostate normal. Extremities not remarkable except for skin lesions and edema and a small tattoo mark on the right forearm. The reflexes were hyperactive and equal throughout.

LABORATORY DATA

Blood	RBC	Hgb.	WBC	Differential
Feb. 15	3,570,000	11.1 Gm.		Juv. 3, Seg. 72, Eos. 13, Lymph. 10, Mono. 2
18			14,600	
19			18,450	
20			16,200	
21			13,500	
26	4,200,000	13.2 Gm	14,100	Juv. 2, Seg. 77, Eos 4, Lymph. 10, Mono 2, Blasts 5

NPN (Feb. 16): 23 mg. per cent
Kahn (Feb. 15): Negative.
Icterus index (Feb. 16): 1.5.
Cholesterol (Feb. 17): 125 mg. per cent.
Urine (four specimens): Acid, negative for albumin and sugar, sediment negative I sp. gr. 1.027 to 1.029.
Stool (Feb. 20): Negative for blood. No parasites or ova.
Electrocardiogram (Feb. 26): Rate 107. Low voltage in all limb leads. Normal QT.

Course: Treatment consisted of forced fluids to 1,000 cc. daily, sulfathiazole 4 Gm. initially followed by 1.5 Gm. every four hours for three days, sodium thiosulfate 10 Gm. intravenously three and four times daily for five days, colloidal baths twice a day, cevitamic acid 50 mg. three times a day.

During the first ten days in the hospital he had a low grade febrile course. The edema increased, the skin became cracked and secondarily infected so that he was treated with sulfathiazole. Blebs on the fingers of the right hand were incised but no pus or drainage was obtained. The distal phalanges of the fourth and fifth fingers of the right hand became gangrenous.

On the 11th hospital day the rectal temperature dropped to 91° F. He became irrational, blood pressure dropped to 80/50 and pulse was imperceptible. He was placed in the shock position, intravenous saline and 500 cc. transfusions were given. He improved mentally, pulse remained around 130 and blood pressure around 90/60. Following this he became very dyspneic and apprehensive, complained that "something was cutting his wind off" just under the costal margin on the right. Examination of the chest revealed suppressed breath sounds over the right lower lobe with slight dullness. There was rigidity of the right upper rectus muscle. Codeine 0.065 Gm. failed to relieve the pain but morphine 0.01 Gm., atropine 0.0003 Gm. and papavarine 0.065 Gm. "quieted" him. He was placed in an oxygen tent. 1,000 cc. of 10 per cent glucose and 600 cc. whole blood were given with little improvement except for a temporary rise in blood pressure up to 102/70. The dullness and suppressed breath sounds became more marked but no râles or rubs were heard. The spasm of the right upper quadrant disappeared. The patient died in peripheral circulatory collapse on the 13th hospital day.

(For diagnosis please turn to page 124)

CASE REPORT - - -

Eosinophilic Granuloma of Bone

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LINCOLN, NEBRASKA

The first description of eosinophilic granuloma of bone as a separate pathologic entity dates back to the year 1940.[1, 2] Since that time approximately 30 cases have been reported in the medical and dental literature. Lesions of this type undoubtedly have been observed previously but were described in terms such as "Myeloma with prevalence of eosinophilic cells" [3] "osteomyelitis with eosinophilic reaction" [4] or otherwise.[5] Today most authors believe that this benign bone lesion is related to Schüller-Christians' and Letterer-Siwe's disease.[2, 6-15]

Jaffé and Lichtenstein [6] consider all three diseases as different clinical expressions of the same basic disorder:

1. Letterer-Siwe disease, which occurs in infancy or early childhood. Its pathologic lesions are widely distributed throughout the soft tissues particularly the lymphoid structures, but also in the skeleton. Histologically the tumors are made up of histiocytes.

2. Schüller-Christians' disease, a chronic variety occurring in children as well as adults, in which the lesions may affect the bone as well as the lungs, heart and central nervous system. In these lesions the histiocytes undergo lipidization, thus being transformed into "foam cells." Some of these cases show involvement of the sphenoid and other bony structures limiting the orbit, thus creating the complete Christians' triad of calvarial defects, exophthalmos and diabetes insipidus.

3. Eosinophilic granuloma of the bone has been described in children and adults aged from ten months to 50 years, the overwhelming majority of whom are males. The lesions are confined to bony structures and may be solitary or multiple. They have been found in almost any bone of the body except for those of the hands and feet. Two cases of eosinophilic granuloma of bone were associated with one of the symptoms of Christians' triad.[12, 15]

Previous case reports have described the anatomic findings as soft grayish-brown bone tumors which microscopically present the presence of eosinophilic granulocytes as an outstanding feature. Histiocytes containing one large round nucleus are seen between these eosinophilic cells. Their cytoplasm may contain phagocytized erythrocytes, granulocytes and hemosiderin pigment. In the vicinity of necrotic areas one encounters giant histiocytes containing sudanophilic droplets, or "foam cells." Jaffé and Lichtenstein [6] believe that these cholesterol-containing foam cells represent secondary engraftments on the histiocytes of inflammatory tissue, which originally was not lipidized. The authors suggest that the lesion takes its course beginning as a histiocytic granuloma which subsequently becomes dominated by eosinophilic granulocytes and at last assumes the character of a lipogranuloma by means of phagocytosis of lipids. Dissolution and restitution follow. They cite one case in which a lesion apparently healed by resolution without first passing through the lipogranulomatous stage. Thoma's report of a case of multiple eosinophilic granulomata [12] seems to support this conception. In his case an early biopsy failed to show eosinophilic cells. The tumor therefore was at first interpreted as that of osteitis fibrosa cystica. A later biopsy from the same site, however, demonstrated typical eosinophilic infiltration of the tissue.

Clinical Symptoms. Local pain though not present in every lesion is the specific clinical symptom. Occasionally the anatomic site of the lesion has given rise to additional symptoms, such as pathologic fractures and in one case complete paraplegia.[11] In two cases [12, 15] diabetes insipidus was an associated finding. Moderate transitory fever has been seen in some of the reported cases.

Laboratory. Laboratory findings have not been helpful. Blood chemical findings have been essentially normal as well as the sedimentation rate. The leukocyte count may or may not be temporarily increased. In the previously reported cases the counts range from 7,000 to 17,000 per mm. of blood. Some cases presented a moderate peripheral eosinophilia but in the majority of the reported cases the differential count was entirely normal.

Diagnosis. The diagnosis of the lesion depends es-

sentially on the histologic examination of a biopsy specimen. Roentgenologically the granulomata appear as solitary or multiple sharply circumscribed bone defects which are found mostly in the skull, ribs and vertebrae, but tumors have been encountered in almost any bone of the body with exception of those of the hands and feet. Secondary periosteal reaction may be seen in cases of pathologic fractures.



FIG. 1. Nodular peribronchial infiltration of both lung fields.

In solitary lesions the differential diagnosis will have to rule out: Ewing's tumor, Schüller-Christian's disease, giant cell tumor, chondroma, chondrosarcoma, osteolytic, osteogenic sarcoma, bone cysts, osteomyelitis, and specific chronic inflammatory lesions such as are seen in syphilis and tuberculosis.

In multiple lesions one has to consider xanthomatosis, Hodgkin's disease, multiple myeloma, and metastases from malignant tumors.

Prognosis and Therapy. The prognosis is good. In only one of the reported cases did the patient die at a later date of unknown cause. After surgical removal and curettage of the bone the majority of the cases received roentgen therapy. However, the experience gathered so far leads one to believe that mere surgical removal of the granuloma represents adequate therapy.

CASE REPORT

Mrs. F. L., a white woman aged 33 years, was seen on July 2, 1916. For a period of three months she had been complaining of pain in the back, somewhat to the left of her spine. After a gradual onset this pain became severe and throbbing in character. Deep inspiration and local pressure aggravated the pain. Talking provoked a dry, hacking and painful cough. During the first month of her complaints the patient had a slightly elevated temperature of 99.2°. There was no loss of weight or appetite.

Ten years ago she had had a febrile disease which involved the majority of her joints with swelling and redness. During the same year she also had pneu-



FIG. 2. Cystic lesion of left 11th rib with pathologic fracture and secondary periosteal reaction.

monia. She had been married for nine years and has one healthy child. The remaining history was noncontributory.

The physical examination showed a well nourished white female weighing 168 pounds, 65½ inches tall and not appearing acutely ill. The body temperature was recorded at 98.6°, the blood pressure was 115 systolic and 70 diastolic.

The head and neck revealed nothing remarkable except for a moderate exophthalmos. The signs of Stellwag, Graefe and Moebius were absent. Neck and thyroid gland were not remarkable.

The thorax was symmetrical but exhibited a marked lag on the left side during the inspiratory phase. A sharp pain in the region of the left 11th rib, two inches from the spinous process prevented the patient from taking a full breath. Palpation of this area was exceedingly painful and marked muscular spasm was felt. There also existed considerable spasm of the left trapezius muscle. Some scattered moist rales were heard over the left lung base.

The heart was normal in size with its apex beat 1 cm. medial of the left midclavicular line. The rhythm was regular at a rate of 84 per minute. No murmurs, thrills or accentuations were noted.

The abdomen showed nothing of note; the liver, spleen and kidneys were not palpable. Rectum and genitalia were not remarkable. The extremities presented no abnormalities; all physiologic deep reflexes were present



FIG 3 Low power magnification. Giant cell in loose granuloma tissue.



FIG 4 High power magnification The same giant cell among eosinophilic leukocytes and inflammatory type cells

X-ray Studies. A routine chest film revealed an extensively distributed small nodular peribronchial thickening throughout both lung fields. (Fig. 1.)

A film of the bony thorax demonstrated a cystic lesion about one inch from the costovertebral articulation of the left 11th rib, causing a pathologic fracture with secondary periosteal reaction. The distal part of the rib had dropped downward, crossing the 12th rib further laterad. (Fig. 2)

No evidence of abnormality was found in the bones of the pelvis, long bones, shoulder or skull.

Laboratory Findings. The urine was negative. The red cell count was 3,800,000, hemoglobin, 12 Gm, leukocyte count 8,250. Differential count showed: segmented forms 64 per cent, staff forms 1 per cent, eosinophiles 2 per cent, lymphocytes 31 per cent, monocytes 2 per cent. The sedimentation rate was recorded at 9 mm. in one hour (Cutler method). The blood calcium was 9.4 mg. per 100 cc., blood phosphorus 3.4 mg. per 100 cc., and blood cholesterol

107.5 mg. per 100 cc. No acid-fast organisms were found in the sputum or stomach contents.

Surgical removal of the bone lesion by curettement yielded a specimen of soft gray, hemorrhagic tissue. Multiple sections of this tissue revealed the picture of a somewhat loose fibrous stroma in which there were many eosinophils. A few noneosinophilic inflammatory type cells were seen, but the predominant cell throughout was the mature eosinophilic leukocyte. Scattered throughout the stroma, also, were islands of pale-staining foam cells and an occasional giant cell. The above histologic changes are characteristic of eosinophilic granuloma of bone. (Fig. 3, 4.) *

The postoperative recovery was uneventful. Roentgen therapy was not administered.

Re-examination after one month: The patient's previous complaints had disappeared. The lung fields presented only a slight amount of residual density in the left base. The previous site of the lesion was healing.

Re-examination after two months: The cystic area in the head of the left 11th rib had been almost entirely filled in. There was apparent additional clearing the pulmonary lesion noted previously.

DISCUSSION

This case of eosinophilic granuloma of bone occurred in a female aged 33. Although at first this type of lesion was believed to be limited to children or adolescents, subsequent cases have been reported in adults. The history and clinical findings were similar to those described in previous cases. This patient had a low-grade fever at the onset of her complaints. Her persistent dry cough upon inspiration and upon talking is explained by pleural irritation, caused by the overlapping of the 11th and 12th ribs due to pathologic fracture.

At the times blood counts were taken no significant peripheral eosinophilia was noted. It therefore remains a matter of speculation as to whether the transitory pulmonary infiltration presented a Loeffler's syndrome.

The lack of roentgen therapy did not seem to delay recovery as compared was irradiated cases.

SUMMARY

1. A case of eosinophilic granuloma of bone is reported in an adult female aged 33 years.

2. Clinical and laboratory findings confirm published observations of other cases.

3. In addition, a transitory pulmonary infiltration was observed.

4. After surgical curettement the lesion healed promptly without the use of roentgen therapy.

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* Report by Frank H. Tanner, M.D., Pathologist, Lincoln General Hospital, Lincoln, Nebraska.

Answer to Quiz Case (page 119)

Diagnosis:

1. Exfoliative dermatitis due to arsenic.
2. Perforation of duodenal ulcer.

Cases from the Medical Grand Rounds of the Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

CASE 26

CAPILLARY BRONCHITIS

DR. HAROLD ELRICK: Mrs. M., No. 569855, is a 53-year-old, white, married housewife, who entered this hospital on April 7, 1947, because of dyspnea and cough.

For the past 40 years, following an attack of whooping cough, she has had a chronic, productive cough with occasional hemoptysis. However, her general health and activity were not restricted until eight years before entry, at which time she had what her physician termed a "heart attack." At that time she had severe dyspnea and weakness, but no chest pain or edema. She spent nine days in an outside hospital and two months at home in bed. At the same time she was started on digitalis which had been continued irregularly until the time of entry.

From the time of her first hospitalization activity has been moderately restricted due to weakness and dyspnea and she has done only light housework. During this same period she has been observed to have a peculiar bluish color to her skin and has had occasional episodes of dyspnea which necessitated several weeks of bed rest. There has never been any chest pain or edema.

Associated with an upper respiratory infection, her dyspnea and weakness increased markedly one week before entry. Her physician treated her with sulfadiazine for several days, and with 300,000 units of penicillin as well, but because there was no improvement she was admitted to the hospital.

Physical examination on entry revealed her to be an obese, extremely orthopneic woman, with a temperature of 102°; pulse of 120; respirations of 30, and blood pressure of 110/70.

The skin had a peculiar purplish, cyanotic hue, and, in addition, there was brownish pigmentation, most marked on the backs of the hands, neck, and in the creases of the palms. There was xanthelasma of the eyelids.

The neck veins were distended. Her chest was filled bilaterally with medium to courses, wet râles from the bases to the apices. Her heart was moderately enlarged to the left, regular, with no significant murmurs. No friction rub was heard. The abdomen was not remarkable. The extremities showed mild clubbing of the fingers and toes, but no edema.

Laboratory examination revealed a red blood cell count of 7.25 million, hemoglobin of 18.5 Gm., a white blood cell count of 7,400 with 87 per cent polymorphonuclear cells.

Her serum CO_2 was 27 m.eq./l.; cholesterol was 298 mg. per cent. Her sputum culture grew alpha hemolytic streptococci.

The electrocardiograms were very unusual. They showed questionable evidence of old posterior myocardial infarction, which was not confirmed by special unipolar leads. I hope Dr. White will say something about that.

The chest films showed extensive, severe, chronic pulmonary disease, fibrosis and bronchiectasis with acute pneumonitis superimposed.

Circulation times arm to lung and arm to tongue, as well as venous pressure, were normal, but they were done some two weeks after entry.

Her course in the hospital has been one of gradual improvement, with subsidence of temperature to normal, and some improvement in her dyspnea. Her color has not changed.

DR. MARIAN W. ROPES: The things to note, I am sure, in seeing her are, chiefly, the cyanosis, which is very definite, and the fact that now at bed rest she is not dyspneic.

DR. WALTER BAUER: She has no valvular disease?

DR. ROPES: No. The color is the combination of the high hemoglobin and residual cyanosis. The cyanosis is less than at the time of admission, but is still obvious. She is comfortable at rest now.

DR. PAUL D. WHITE: Are the neck veins distended now?

DR. ROPES: The neck veins have not been distended



FIGURE 1

since the first two or three days, but were definitely distended during the first 24 hours. I neglected to say that there is definite pigmentation, rather generalized, and she does have increased pigmentation in the creases of her hands. There is no other definite localized pigmentation.

DR. BAUER: What is the character of her breathing? Asthmatic?

DR. ROPES: No. There are many râles still persistent, but not moist râles and the breath sounds are not particularly emphysematous in character.

DR. JAMES H. MILANS: Does she have dry râles now?

DR. ROPES: Now, yes. She had a great many moist râles at the time of admission. She has diffuse markings which by x-ray have not changed greatly.

The x-ray department suggested that the heart (Fig. 1), by x-ray, was suggestive of cor pulmonale, which I think is of interest, because to me one of the interesting features of this patient is, in the first place, the contrast with the man who was shown two weeks ago, in whom there was very marked dyspnea with exercise, and little, if any, cyanosis, and in whom there is really little question, that there is pulmonary arterial disease; whereas, in this patient, there is little or no evidence that there is any pulmonary arterial disease, but very marked chronic pulmonary disease, and the cyanosis and presumably the elevated hemoglobin and red cell count are related to that. The absence of any definite evidence of cor pulmonale, after 39 years of disease which has been of these severity recently, is interesting and I would be interested in Dr. White's comment on that.

DR. WHITE: Dr. Paul and Dr. Williams have already commented about this very odd electrocardiogram (Fig. 2). It is not any pattern that we can recognize offhand, certainly. It is not that of the cor pulmonale alone, but there may be something added. In other words, there may be a combination of factors here which would conceal the pattern of a simple cor pulmonale, that is, there may be actual myocardial disease of some nature. Neither is the record characteristic of myocardial infarction. The S waves are a little wide with an apparent left axis deviation, but their width, I think, indicates some abnormality of the muscle and not simply a preponderance of one ventricle or the other. I believe that it is impossible to analyze this record further without knowing more about her heart muscle.

DR. LAURENCE L. ROBBINS: Did you say, Dr. White, that this was left axis deviation?

DR. WHITE: Yes, so far as the electrocardiogram indicates, but it is not the usual left axis deviation. It suggests muscle involvement and not simply hypertrophy or enlargement of either ventricle.

DR. ROBBINS: I would have thought from looking at the films that the patient probably had a chronic cor pulmonale because of what appears to be a long-standing pulmonary fibrosis with probable emphysema, and these people usually develop some right ventricular hypertrophy. I wonder if any of this can be because the heart is a little bit to the left?

DR. WHITE: The displacement of the heart could have some influence.

DR. BAUER: Could it be due to mediastinal adhesions?

DR. ROBBINS: I don't believe so, because there appears to be enough collapse in the left lower lobe so that the heart could be displaced. I would think it was a chronic process and, in all likelihood, what is going on in the left lower lobe could be an acute process. I remember a similar case some years ago of a patient with cor pulmonale who became decompensated during an acute pulmonary episode of pneumonia. I wondered a little bit when I first saw these films if this might not be a similar type of thing.

DR. WHITE: It was suggested that she may have had heart trouble some years ago, perhaps coronary heart disease.

DR. ROPES: The story sounded more like some sort of episode with just dyspnea and nothing else following it.

DR. WHITE: It is possible that she may have had some heart disease involving the myocardium, either coronary or some diffuse infectious process, which could distort the record and so make it impossible to be used to decide whether there is a cor pulmonale or not.

Does the pigmentation mean anything? Has she had any liver dysfunction? Is there any possibility of hemochromatosis?

DR. ROPES: Actually we have not done liver function tests on her. We have not explained the pigmentation.

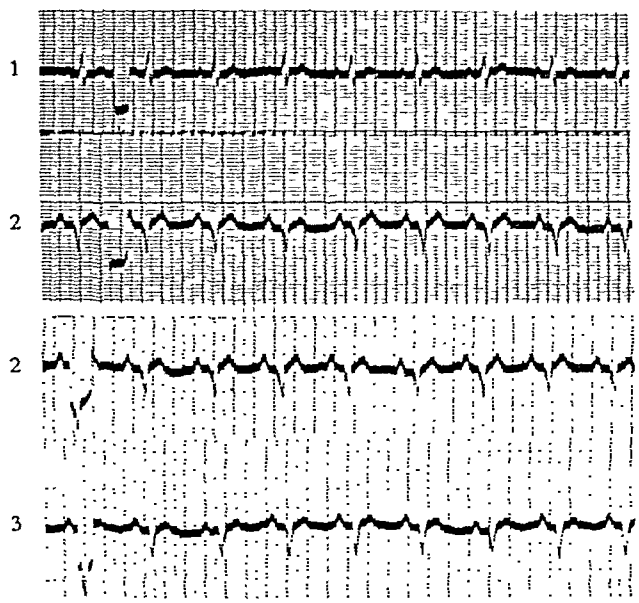


FIGURE 2A

DR. WHITE: A condition such as hemochromatosis can affect the myocardium diffusely and, if so, present a picture resembling this. I think that there is something more in the myocardium here than simply enlargement.

DR. HELEN S. PITTMAN: Haven't we felt right along that one did not get true cor pulmonale except in the presence of coronary disease? We have followed a good many of these people with extensive fibrosis and they haven't had cor pulmonale.

DR. BAUER: While I was on service we had three come in with acute congestive failure, where you could not find any other explanation than acute pulmonary fibrosis plus emphysema; plus one fellow, who as a butcher did a pretty heavy load of work. You remember those three, Dr. Kreisle?

DR. JAMES E. KREISLE: Very similar.

DR. WHITE: The most common cor pulmonale comes with silicosis or pulmonary arterial disease, but there are lesser gradations of the cor pulmonale. If you could dissect off the right ventricle and weigh it, you would find it is not infrequently enlarged with chronic pulmonary disease, such as emphysema and asthma.

DR. BENJAMIN CASTLEMAN: We see it often with asthma and emphysema, but I don't believe they have the high red count and cyanosis.

DR. WHITE: But the pulmonary disease could do that. An extensive fibrosis could affect the pulmonary vessels.

DR. BAUER: You are not going to argue that you

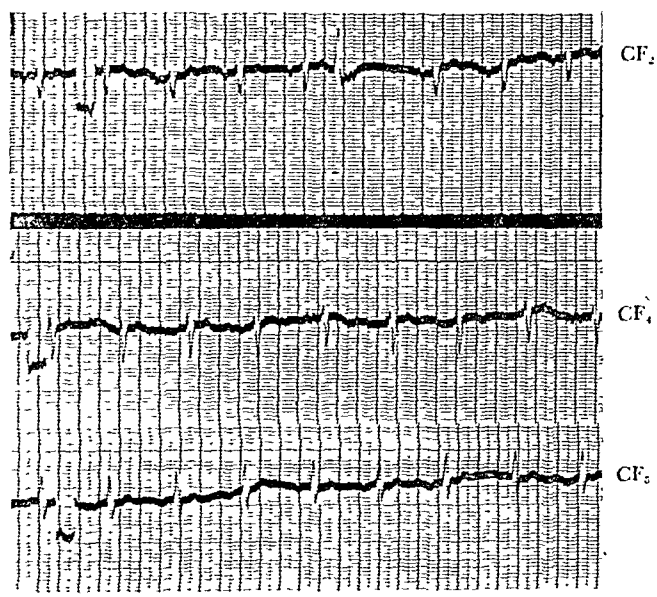


FIGURE 2B

have to have pulmonary vascular disease in order to have an increased red blood cell count?

DR. CASTLEMAN: Not up to the seven and eight million cells that they have with the cyanosis. I don't believe we have seen them without vascular disease.

DR. WHITE: I believe that vascular disease can accompany pulmonary fibrosis.

DR. CASTLEMAN: Yes.

DR. WHITE: The most extensive cyanosis is that of the "black cardiacs" but actually in them, the cyanosis is due chiefly to the pulmonary disease, and not to the heart disease.

DR. ALLAN M. BUTLER: What is the vital capacity of this patient?

DR. ROPES: We don't know.

DR. JOSEPH C. AUB: Why should she have such a high red count and normal CO_2?

DR. ROPES: I would like an explanation of that.

DR. BUTLER: That is why I would like to see what the vital capacity is.

DR. WHITE: Dr. Altschule, have you any comment about the electrocardiogram?

DR. ROPLS: We were interested in this patient because, while she does not represent the typical patient with pulmonary edema without cardiac disease, she approaches that group. In this case, the evidence of left ventricular insufficiency is slight and not the cause of what we interpreted as pulmonary edema following her acute superimposed infection. I hope Dr. Altschule will discuss the factors involved.

DR. MARK D. ALTSCHULE: The electrocardiogram, like all the rest of the data, is so markedly atypical that, I think, it is fortunate that this type of case is so rare. Because, no matter what diagnosis one makes in life, it is likely to be proved wrong when the patient is examined subsequently.

I suppose the main question at issue here is whether or not this patient has, or has had, left ventricular failure. I do not believe that that is a question which anybody can answer. The concept that left ventricular failure is the sole or chief cause of pulmonary edema is one which has been developed and usually accepted by clinicians, whereas, to my knowledge, there is no physiologist in the world who will accept that concept. We, therefore, have a paradoxical situation in which the clinician uses a physiologic concept to explain a clinical finding—a physiologic concept which no physiologist will accept. The physiologist, on the other hand, refers to the syndrome merely as a pulmonary edema, which is a clinical concept. That paradox exists, and in this case, my money is on the physiologist.

As most of you undoubtedly know, there is a large amount of experimental physiologic work which shows that factors other than left ventricular failure give rise to pulmonary edema, and that, as most of you also know, or should know, the physiologic work which is said to demonstrate left ventricular failure as the cause of pulmonary edema is small in amount and pretty poor in quality. Unfortunately, one of the early papers on the relation of pulmonary edema to left ventricular failure, and vice versa, was written by a very famous man, namely, Welch. It must be pointed out, however, that he did that work back in 1867, when he was a student in Germany and in so far as that specific project is concerned, the work which he published, and everything similar done subsequent to his time, is mighty poor; it is a pretty weak crutch on which to lean in attempting to support the concept of left ventricular failure as the sole or chief cause of pulmonary edema.

In regard to this case specifically, I do not think you can ever decide whether it was left ventricular failure or not. It is important, I think, to realize that the only physiologically established factors which can produce pulmonary edema fall into two main categories. One of them, embracing a very large amount of work—somewhere around 50 published papers, most of them of good quality—involves the neurogenic mechanisms. That concept is not very well formulated except in the minds of the people who are working in the field, but the concept in general involves a consideration of a primary or secondary vasomotor disturbance of the lung, which ultimately leads to transudation of fluid and the development of pulmonary edema. Neurogenic factors which have been described involve stimulation of certain parts of the brain and various traumatic conditions—the cerebral form of pulmonary edema made prominent by the Viennese about 40 years ago. Another group of neurogenic factors seems to involve reflexes from the heart and aorta, and parts of the lung and, possibly, some other viscera.

The example of pulmonary edema due to a direct damaging lesion involving the capillaries and epithelium of the lungs has usually been war-gas poisoning—phosgene, chlorine, or something of that sort. However, during the last war, it was shown quite definitely that even in the case of phosgene or chlorine intoxication in animals, pulmonary edema did not develop if the lungs were first denervated, so that the concept of a direct damaging lesion as the cause of pulmonary edema is on a most insecure basis even in that instance.

What the nature of the specific change which results in this vasomotor disturbance is, is not very well known. That is not at all unexpected because no two people will agree upon what the normal vasomotor regulation of the lung is, and, therefore, it is not at all surprising that nobody can agree on what the disturbance of vasomotor regulation might be. At any rate, there is that large body of physiologic evidence which can be fitted in with certain clinical syndromes. The most recent work, that of Dr. Luisada, involved the production of acute pulmonary edema in dogs by causing sudden distension or marked distension of the carotid sinus. If the carotid sinus were denervated, this pulmonary edema did not occur. I saw the dogs and I saw the pulmonary edema, and it looked like the real thing. Those experiments may have some bearing on some of the cases of pulmonary edema in patients with aortic insufficiency or with hypertension, or something of that sort.

Another physiologic mechanism or group of mechanisms involves anoxia. There is some excellent work done by Drinker and his group which clearly demonstrates that the transudation of fluid in the lung is greatly increased when the lungs are made anoxic. The capillaries of the lung are very unusual in many respects but especially in one, and that is that the blood with which they are bathed is markedly venous in type, so they receive most of their oxygen actually from the outside air; therefore, cutting down the oxygen content of the air which comes in contact with the alveolar surface and capillaries produces anoxia. Judging by the physiologic work of Drinker and others, it may give rise to an increased transudation of fluid. *Increased transudation of fluid does not necessarily* mean edema, because the lymphatic mechanism for carrying off the fluid in the lungs is very well developed. However, if something interferes with the carrying off of the fluid—lymphatic blockage associated with infection, or something of that sort—one would develop pulmonary edema under those conditions. I think it is very easy to imagine that any patient with chronic bronchitis or bronchiectasis, perhaps with superimposed acute infection, might have his lung lymphatics develop some type of at least temporary obstruction since they run close to the bronchioles, and therefore, one might get the picture of pulmonary edema in a patient of that sort.

Now, actually, this patient probably has some type of strain upon the left ventricle. It used to be believed that cor pulmonale was due solely to an increase in pressure in the pulmonary vascular bed, due to one type of disease or another, which resulted in right ventricular strain. There have been several excellent studies from England and also from New York, which show that in patients who have cor pulmonale the cardiac output, which means the output of both left and right ventricles, is markedly increased. Actually, that is what we would expect in a patient with anoxia. We know anoxia increases the cardiac work, and that is one of the compensatory mechanisms which take care of the effects of anoxia. In cor pulmonale, there may or may not be increased pressure in the pulmonary vascular bed, but the anoxia is present and increases the strain on both ventricles, and that accounts for some of the studies which show hypertrophy of the left as well as the right ventricle. Therefore, one can place cor pulmonale, or congestive failure due to pulmonary disease, in somewhat the same category as congestive failure due to thyrotoxicosis, or anemia, or beriberi, and so forth, where much of the strain is related to an increase in cardiac output which persists for days, weeks, months or years. Now what factor determines whether a specific patient will develop signs of failure while others do not is, of course, unknown, but in view of the fact that many patients with cor pulmonale of this type are in the coronary artery age-group, one suspects, and one can demonstrate, the coronary factor. In others, hypertension is present, and so forth. I believe that one cannot expect uniformity in the production of cor pulmonale in patients with severe pulmonary disease and severe anoxia.

I am not sure that this patient has any important degree of heart disease and I am not sure from the description that she now has or ever had pulmonary edema in the clinical sense. Since she had inflammation, she must have some edema here and there in the pathologic sense, but I am not sure that the syndrome which brought her in and which she had previously is that of acute pulmonary edema, as we know it clinically.

I think it might be of interest, in that case, to inquire into the origin of her extreme cyanosis. We see cyanosis in patients with severe pulmonary disease under a variety of circumstances. A patient who has marked emphysema with a large increase in residual air which does not move during respiration, has difficulty in changing that residual air by diffusion and mixing, and, therefore, can be anoxic solely on the basis of severe emphysema. This patient does not fall into that category and although she may have some impairment of her ability to mix air within the lungs, I do not believe that is a primary factor.

A second large group of patients with pulmonary disease who have cyanosis have very marked fibrotic changes, so that the expansibility of the lung is markedly impaired. I don't think she has that much fibrosis, either from her appearance or the type of respiration she has, or from the x-ray picture, although she undoubtedly has some and that also is a contributory factor.

A third large group of patients with cyanosis due to chronic pulmonary disease are those who have obstruction, the most common type being obstruction due to chronic bronchial asthma. There is another much less common type within this group in which obstruction is generalized and severe and is not due to spasm or damage involving the larger bronchi. The damage is to a large extent, or almost entirely, in the terminal bronchioles, and that syndrome is referred to as bronchiolitis fibrosa obliterans. The pathologist will agree that almost any patient who has chronic inflammatory change in the lung will have small patches of that lesion here and there. It is very unusual to have the lesion exist in a widespread form, but it does occur.

The precursor of that lesion is very often—it is dangerous to refer to something occurring often in a rare syndrome—but relatively often the precursor is a condition which has pretty largely dropped out of the more modern textbooks. The older textbooks referred to it as capillary bronchitis, which is a disease or a syndrome of infectious nature, with the involvement in the smallest bronchioles. These patients have innumerable fine or moderate moist râles heard widely through both lungs; they have a severe degree of cyanosis and marked dyspnea; and, in association with the anoxia and fever, may go into collapse at times. That sounds very much like what this patient had eight years ago and what she had again recently. If healing is complete, the patient may suffer no subsequent difficulty, but if the healing is incomplete, he ends up with more or less cyanosis and dyspnea, due to obstruction in the smaller airways. I suspect that this patient, if she falls into the hands of a competent pathologist, will be found to have a severe degree of small bronchiolar obstruction due to this fibrous lesion which represents the organization of granulation tissue.

The differential between capillary bronchitis and pulmonary edema is a very difficult one and very often not made. On the other hand, it is an important one, because the treatment of acute pulmonary edema is the injection of morphine in fairly large doses, 15 or 30 mg., whereas the giving of doses of morphine of that size to patients with severe pulmonary disease and cyanosis and dyspnea may cure the dyspnea, but only by terminating respiration completely. The differentiation, from the point of view of the patient at least, is an important one. There is one clinical finding which is at times helpful in making that differentiation. The extreme degree of cyanosis which a patient with a syndrome of capillary bronchitis shows is far greater than the cyanosis which a patient with acute pulmonary edema has with that number of râles and that degree of fever. The patient with pulmonary edema is cyanotic, of course. He has a pale, ghastly color, whereas the patient with capillary bronchitis is a lot bluer and, in a general way, the only time patients with pulmonary edema get that blue is when they are dead or close to it. An extreme degree of cyanosis should make one hesitate to give large amounts of morphine if the diagnosis is in doubt.

As I say, I suspect that that has been the situation in this case but I don't know. She may very well have various myocardial stresses and strains which might give rise to pulmonary edema, but that again does not tell us anything about the mechanism which might be involved. I think, from the point of view of the physiologist, and I think it is desirable also that the clinicians take that point of view, the term "left ventricular failure" should be used rarely, if at all, because it implies a certainty and a security which cannot exist, and, on the basis of physiologic work, does not exist. I think it is much better to refer to the syndrome as acute pulmonary edema and let it go at that, and leave it to the passage of time and the endeavors of appropriately trained men to work out the exact mechanism. For the time being, I think, most physiologists will regard the nonanoxic type of pulmonary edema as reflex in origin and involving the vagus nerve, and therefore, it might appropriately be referred to as vaguely vagal in origin.

DR. MAURICE FRIEDMONT-SMITH: Dr. Altschule, from the point of view of the physiologist, what other treatment of acute pulmonary edema is indicated besides morphine?

DR. ALTSCHULE: Oxygen, of course.

DR. FRIEDMONT-SMITH: Bleeding? Tourniquets?

DR. ALTSCHULE: In all the experiments where the studies were made, it has been demonstrated that, irrespective of the origin or mechanism of pulmonary edema, anything which decreases the inflow of blood into the lungs will favor recovery, and that includes tourniquets, and venesection, and of course, positive pressure respiration. It may be pointed out that positive pressure respiration does not act by squeezing the edema fluid back into the capillaries. If it did that, it would stop the circulation completely. Tourniquets on all four extremities decrease the circulating blood volume and retard the entry of blood into the thorax. It does not matter what you believe the mechanism of pulmonary edema is—you treat it the same way irrespective of theoretical considerations.

I think it is important to bear in mind, also, that in addition to the vasomotor disturbance of acute pulmonary edema there is a disturbance in bronchial motility. Dr. Soma Weiss injected the vagus nerve on one side and cured pulmonary edema; the patient had it bilaterally and he cured it in one side by injecting novocaine there. We therefore, in order to form a unified concept, had better stick to a neurogenic mechanism for the time being.

DR. WHITE: You do not rule out left ventricular failure as a common cause of pulmonary edema, do you?

DR. ALTSCHULE: Left ventricular disease is very commonly associated with pulmonary edema.

DR. WHITE: When you have a patient with hypertension of long standing, cardiac enlargement and engorgement of lung hilus shadows and dyspnea on mild exertion and on first lying down at night, that

patient presumably has dyspnea because of heart failure and heart weakness. Would you agree that dyspnea of that sort is due to the heart weakness although superimposed on that there can be a neurogenic or some other factor to produce pulmonary edema and cardiac asthma?

DR. ALTSCHULE: There is not much doubt of it. Most of the attacks of pulmonary edema we see occur in patients who also have chronic congestive failure. That bears out what you say. It also makes the clinical point that if you treat chronic congestive failure the patients very often stop having the recurrent paroxysms. On the other hand, many patients who have the paroxysms of pulmonary edema get over them without any treatment. Many patients come into the hospital with a history of having had them every night and having gotten over them without any treatment.

DR. WHITE: May I add that in most of the cases of cor pulmonale that I have seen there has been no pulmonary edema. When such a heart fails, there is enlargement of the liver and dependent edema, but I do not see the cor pulmonale associated with pulmonary edema. With pulmonary embolism and the acute cor pulmonale, on the other hand, there may be an attack of pulmonary edema due to the pulmonary involvement as you suggest; but the majority of the cases of chronic cor pulmonale do not have pulmonary edema.

DR. ALTSCHULE: It is hard to differentiate pulmonary edema from other things which happen to those patients, because by the time they have cor pulmonale they are often dyspneic all the time, and it is hard to make out the increase in such dyspnea. We have had a few patients who were not asthmatic primarily—in whom cor pulmonale developed on the basis of emphysema—and during their course, repeated recurrent paroxysms of increased dyspnea and râles and wheezing occurred, which responded to aminophylline intravenously. We thought they might be considered as examples of so-called left ventricular failure or at least pulmonary edema in patients with cor pulmonale. The syndrome of cardiopulmonary failure, where most of the strain is considered to be on the right ventricle, not infrequently terminates in frank attacks of acute pulmonary edema or cardiac asthma.

DR. BAUER: The term, bronchiolitis, is often used, but I think it is a hard diagnosis to prove clinically and I think the pediatricians use it much more often than we internists do. How can you prove it clinically? It is a very difficult thing to prove.

DR. ALTSCHULE: If you have a patient with marked cyanosis who does not have severe emphysema or extensive fibrosis, and does not have pulmonary obstruction such as is caused by bronchial spasm, I think there are very few causes, aside from obstruction of the small bronchioles, particularly where a patient has a lot of very fine râles widely distributed.

DR. BAUER: How do you distinguish it from certain cases of primary pneumonia, where you can have moist râles throughout both lungs with no x-ray evidence of consolidation, or very small areas which may again disappear in a few days? You may say they are misdiagnosed, they are not primary typical pneumonia, but certainly we see such things during an epidemic of primary pneumonia.

DR. ALTSCHULE: If the cyanosis were extreme and the râles numerous and widely heard, I would say that the cyanosis and the râles were due to involvement of the smallest bronchioles.

DR. BAUER: The alveoli in those cases contained a lot of fluid found at post mortem, and I don't think one needs to presuppose the smallest bronchioles involved.

DR. ALTSCHULE: You can establish that only by what happened to the patient over a period of time.

DR. BAUER: You see the same people six months or a year later or two years later and they have no evidence of any residual pulmonary disease. They are back on duty, doing a full job. I think it would be very hard to distinguish that from this thing called acute bronchiolitis.

DR. ALTSCHULE: It undoubtedly is.

DR. CASTLEMAN: Did they have cyanosis?

DR. BAUER: Yes.

DR. ALTSCHULE: I would be very much interested to know what the small bronchioles showed.

DR. BUTLER: In pediatrics, what you are describing is what we would call interstitial pneumonia; pathologically, there is interstitial infiltration around the small bronchioles, and we picture it as an obstruction of the small bronchioles, not a disease which primarily affects the alveoli.

DR. BAUER: That is all true, but to say that these things necessarily go on, that it is an irreversible process, is wrong.

DR. ALTSCHULE: Oh, by no means is it irreversible.

DR. BAUER: You implied that at one point.

DR. ALTSCHULE: Well, I withdraw that implication.

DR. BAUER: There is no doubt about having interstitial pneumonia and about having peribronchial changes which can be seen in these people at post mortem, even at the end of a few days' illness, but it is not an irreversible process. There is evidence of that.

Editor's Follow-up Note

This patient was discharged on the 1st of May 1947 improved from her admission status, but not cured. On two follow-up visits to the Medical Outpatient Department on the 18th of May and the 7th of July the patient was making slow, steady improvement symptomatically with a gradual weight loss for her obesity. At her last examination she still had minimal cyanosis with medium and coarse râles from the bases to the midscapulae bilaterally. In general it was the opinion of the examiner that she was doing about as well as could be expected in the face of her long-standing disease.

CASE 27

Cor Pulmonale

Dr. Myles Baker: The service is presenting one case of what we took to be an instance of right ventricular hypertrophy and failure of undetermined etiology. The case has given rise to a good deal of discussion on a previous admission here about eight months ago. Dr. Bliss will review it. It is a rather long story and he will review it briefly.

Dr. Harry Bliss: Mr. S., No. 111081, a 30-year-old white male, was first seen in this hospital in 1938, at which time he came into the Orthopedic Clinic complaining of aches and pains in his right leg. It was found that the saphenous vein on the right side was considerably dilated, and the dorsalis pedis pulse and posterior tibial pulse on the right were not palpable. He persisted in having these complaints and in 1940 developed ulcers of both ankles, which healed slowly under local therapy.

He was again seen in 1941 when he was admitted to the Surgical Service for bilateral saphenous ligation. This was performed and about a month later the ulcers on his ankles broke down. He was readmitted to the Surgical Service and at that time a bilateral lumbar sympathectomy was performed and skin grafts applied to the ulcers. The pathologic section of the skin removed at the time of grafting showed thromboangiitis obliterans. He was discharged with his ulcers healed and followed in the Outpatient Department because of positive serologic tests which had been found at the time of admission. At that time he received 37 injections of bismuth and 32 of arsenic. A spinal fluid gold sol curve done before and after treatment revealed ten zeros. He had negative spinal fluid serologic tests at all times. During the course of his treatment with arsenic and bismuth he had an albuminuria which has not recurred. He also had an episode of what was probably arsenical hepatitis.

In 1945 physical examination in the Outpatient Department showed that the patient had bilateral mild edema of the ankles but no ulcers; a normal nasal septum, no cardiac murmurs and no enlargement of the heart.

In 1946 he was admitted to the Medical Service for the first time. At the time of entry he complained of hemoptysis of about a cupful of bright red blood on the morning of admission. He gave a history of no rheumatic fever and said he had had bilateral edema of the ankles for many years, although that had not been noticed in the Outpatient Department prior to 1945. He also said he had been dyspneic on exertion for at least one year.

On physical examination he was pale. There was massive pitting edema up to his xyphoid process. He was in no particular respiratory distress. His nasal septum had a large perforation. There was a large pulsating neck vein and also an arterial pulsation on the right side of his neck. There was a very slight pulsation on the left side of his neck, probably venous. The right radial pulse was nearly imperceptible. The heart was enlarged about 10.5 or 11 cm. to the left of the midsternal line, and a grade 3 basal systolic murmur was heard. P_2 was greater than A_2. The cardiac rhythm was regular and there was no evidence of a diastolic murmur. The liver was not palpable. His total serum protein was 5.3 Gm. with 3 Gm. of serum albumin. The venous blood pressure was 320 mm. of water in the left arm and 300 mm. in the right arm. The circulation time was 32 seconds with decholin; the vital capacity was about 2.6 liters. An electrocardiogram showed right axis deviation with evidence of right ventricular strain. He had a good diuresis with digitalis. He was given a low-sodium diet as well as mercupurin, and lost 22 pounds during his hospital admission. At that time his hemoptysis was investigated and no evidence of tuberculosis by guinea-pig culture or by smear of sputum was found, although there was a family history of tuberculosis. He was discharged feeling reasonably well and went home to lead a quiet life.

He was readmitted in October 1946, at which time the physical examination was essentially unchanged, except for the fact that his liver had become palpable during the interval. The laboratory examinations were relatively unchanged. He was again discharged on the same regimen and returned here on April 4, 1947, this time complaining of another hemoptysis of about a pint. He has been relatively well on the service and has been maintained on the same regimen. His hemoglobin and red count are relatively

normal and the rest of his tests are about the same as before.

DR. BAKER: I think the outstanding observations on physical examination are: the lack of any pronounced cyanosis; the lack of pronounced dyspnea, certainly at rest. There is this venous distension in the neck, of which Dr. Bliss spoke. The heart, as you see by the x-ray (Fig. 1), is enlarged. There is a not very impressive grade 2 systolic murmur at the apex and along the left sternal border. There has never been any gallop rhythm heard, to my knowledge. When he came in, he had pitting edema of both legs and well up his back, and even now has pitting edema above the sacrum.

DR. ROBERT S. PALMER: Did he have fever off and on during this long course?

DR. BAKER: No, I don't think he did, Dr. Palmer. He has been pretty short-winded, but says he went for a half-mile walk the other day and has been hunting in the swamps.

DR. PAUL D. WHITE: He has no clubbing?

DR. BAKER: No clubbing. Dr. Schulz, would you like to go over the x-rays?

DR. MILFORD SCHULZ: Yes.

DR. WYMAN RICHARDSON: Has he been exposed to benzol?

DR. BAKER: Not that I remember.

DR. JAMES H. MEANS: Dr. Baker, I remember him very well, and one of the things that impressed us has been the lack of cyanosis. We thought he ought to be cyanotic and both Dr. Adams and I thought now when he came in that he looked a little cyanotic from this distance. I didn't get a chance to see him up close.

DR. BAKER: I thought his lips were a little cyanotic.

DR. MEANS: We were rather impressed with not finding cyanosis on the previous entry.

DR. SCHULZ: The chest films show an obvious enlargement of the heart. How much of this is due to the right heart, I don't know. The right heart can be considerably enlarged at the expense of the left heart. He has a prominent pulmonary artery. He has never had evidence of pulmonary congestion so far as the films are concerned.

DR. WHITE: The right hilus is not very prominent, is it?

DR. SCHULZ: No, it is a little queer considering the size of the left. In fact, it is almost small.

DR. BAKER: During his previous admission, the service had considered the differential diagnosis as between congenital heart lesion and some cause, possibly intrapulmonary and arterial in nature, that would give rise to right ventricular hypertrophy. I did want to ask Dr. White whether he felt we had been able to exclude the possibility of a congenital lesion here? Perhaps auricular septal defect?



FIGURE 1

DR. WHITE: The only condition besides chronic cor pulmonale that this could resemble from the x-ray picture, although that is not characteristic either, would be an auricular septal defect in which the hilar shadows as well as the pulmonary artery are prominent. The hilar shadows are, however, not prominent enough, from my experience with these cases, to feel at all sure about an auricular septal defect.

DR. BAKER: Dr. Dexter has come over from the Peter Bent Brigham Hospital to aid in elucidating this problem.

DR. LEWIS DEXTER: I am not sure that I am going to be able to add anything here except perhaps to suggest a few things. Here is a young man 30 years old who has a past history of thrombo-angiitis obliterans as well as of syphilis. He comes in with chronic cor pulmonale as the presenting picture. It seems to me there are three things, or possibly more, that may be causing his disability and I am not sure that it is very easy to tell which one is responsible. One possibility is that he has a congenital cardiac lesion and, as Dr. White has said, an auricular defect would certainly be the most likely. But the lack of hilar congestion, I think, is very much against this diagnosis because it

should be readily apparent with his degree of cardiac failure. A combined defect, such as tetralogy of Fallot plus a ductus arteriosus, might be postulated. This would account for many of the findings, including right axis deviation and cardiac failure. With this combination of lesions, there is usually more of a left-sided heart failure than right.

It is interesting to speculate with regard to the possibility of pulmonary vascular disease. This man has two of the possible etiologies for these. The first is syphilis; Ayerza's disease is supposed to be a syphilitic endarteritis of the pulmonary vessels. It is excessively rare, and I would doubt its presence in this patient. The other is thrombo-angiitis obliterans, which has been reported to involve the pulmonary vessels. When this involvement is extensive, signs of chronic cor pulmonale, as this man has, may be present. Thrombo angiitis obliterans may also involve the coronary vessels and be an added factor responsible for his cardiac failure. Could this be an adhesive pericarditis with a big heart? I see little to suggest such a possibility. Sometimes, however, it gives rise to right axis deviation, which this patient has.

The venous catheter has turned out to be very helpful in the recognition of some of these disorders. It is useful in recognizing some of the major defects in congenital heart disease. Although I recently wrote Dr. Means, and also Dr. White, that it was of no value at all in the diagnosis of constrictive pericarditis, recent studies have indicated that in cardiac tamponade the pulse pressure in the right ventricle becomes narrow instead of wide as is seen in other types of cardiac failure. A narrow pulse pressure in the right ventricle would be very suggestive of constrictive pericarditis in this individual. I am not willing at this time to say that it would be diagnostic because we have only three cases. I think, however, that it may prove to be quite useful in picking up early constrictive pericarditis.

Pulmonocardiac disease is very difficult to recognize clinically, and it presents a clinical picture identical with what this man has. This patient has evidences of chronic cor pulmonale; he has a loud P_2; the right side of his heart is apparently enlarged; he has right axis deviation by electrocardiogram. He has distended neck veins, a large liver, edema, a very high venous pressure. Clinically, it is often impossible to tell whether this is a result of left heart failure with back pressure through the pulmonary circuit, or whether it is primarily in the lung. The venous catheter gives promise of being helpful. We have had one proved case of primary pulmonary vascular disease and two others we believe were such. In these cases the pressure in the pulmonary artery may be very elevated.

I would suspect that this man has a generalized thrombo-angiitis obliterans which has involved his pulmonary vessels. I think it is a good working hypothesis, at least.

DR. WHITE: Although that diagnosis, it seems to me, is the most likely one, it is pretty rare. I have written to some people who work with endarteritis obliterans in the legs and they have rarely seen it in the lungs. I would like to raise the possibility of pulmonary embolism, which has been massive and recurrent, especially since the veins are involved. He may have had leg vein thrombosis which has given him chronic pulmonary arterial obstruction due to embolism. I think that that is less likely, however, than pulmonary endarteritis obliterans.

DR. MEANS: Would you add to the list also the possibility of pulmonary thrombosis? You remember we had one who had intensive thrombosis of the pulmonary artery that nearly killed him.

DR. WHITE: It did not start as an embolism?

DR. MEANS: No It might have started on top of this kind of thrombosis. That is by definition a thrombus. The one we saw nearly occluded the pulmonary artery and gave some moderate cyanosis. One of the things that bothered us was why this fellow wasn't more cyanotic. Do you want to say anything about that, Dr. Dexter, in relation to pulmonary artery disease? When do you and when don't you get cyanosis under these circumstances?

DR. DEXTER: I don't know, Dr. Means. Certain patients have dyspnea all out of proportion to any other findings at all; they are just breathless; they cannot roll over in bed without getting out of breath, and they don't necessarily have to be cyanotic. There are others who will be rather deeply cyanotic and will not be terribly out of breath at rest. I don't know the answer. Do you, Dr. White?

DR. WHITE: It seems to me that the dyspnea and cyanosis in many of these cases are due chiefly to the severe chronic pulmonary disease itself which is at the basis of a good many cases of cor pulmonale. Silicosis is an example. There the pulmonary disease *per se* is more the cause of the cyanosis than either the pulmonary vascular disease or the heart disease. With the cor pulmonale, the lungs are not badly affected but the circulatory system is at fault, with involvement of the small vessels. Cyanosis need not appear until the right heart fails and a peripheral venous stasis develops.

DR. JOSEPH C. AUB: Ought you not be talking more

about the pulse on the right side of the neck and not on the left as part of bringing it into your diagnosis?

DR. WHITE: Of course, he has tremendous venous pressure but there is often an asymmetry of the neck veins. The veins are almost always more pronounced on the right side than on the left; the jugular bulb is there and so swells up more than do the venous channels on the left.

DR. PALMER: Did you mean by the systemic veins to include the mesenteric veins and how much of this picture could be explained by venous obstruction due to vascular thrombosis?

DR. DEXTER: You mean pulmonary veins or systemic veins?

DR. PALMER: The visceral veins of the liver and spleen.

DR. DEXTER: The venous pressure in his arms and legs, if I understand your question correctly, is the same, as I understand it, so that I think you would have to go back to the heart as the source of the high venous pressure. These patients with thrombo-angiitis obliterans are prone to have not only an arteritis but also a phlebitis.

DR. RICHARDSON: Have you considered specific therapy in this case? Anticoagulant therapy, in other words?

DR. DEXTER: I am afraid I have not. I do not know whether that has been applied successfully or very impressively, at least, to thrombo-angiitis obliterans. Can you tell me?

DR. RICHARDSON: No. I am conservative about it. I am trying to be persuaded.

Editor's Follow-up Note

This patient was discharged on the 11th of April 1947, at which time he was improved but not asymptomatic. On a follow-up visit to the Cardiac Outpatient Department on the 30th of April he was found to be in moderate failure again, because of which his mercupurin was increased from two to three doses weekly and he was continued on a low-sodium diet, digitalis, and 15 Gm. of urea t.i.d.

Several follow-up visits to the Outpatient Department as well as two short hospital stays for cellulitis in his right leg revealed his cardio-pulmonary status to be about as on discharge in April. It seemed unlikely that there would be any significant improvement in the fundamental disease.

COMMUNICATION

Sir:

I am writing to comment on the article on "Trends in Immunization of Children" appearing in the June issue of the AMERICAN PRACTITIONER.

The article was excellent until the writer stated that there was no use giving typhoid immunizations in most of the children. I strongly disagree, and think that all small town and rural infants should be immunized against typhoid (triple vaccine) before they are allowed to crawl. Only recently have we been able to obtain triple vaccine for use in the County Health Department. I have had one case of para-typhoid fever this summer after so-called immunization with the single vaccine. Evidently the writer does not know that typhoid has only recently ceased to be a major disease in the rural South; I mean in the last 25 years. Many men are still carriers. Only 40 per cent of the rural homes have any sort of privy. In many of these, the men regard the privy for the women and children and routinely defecate in a stall. This leads to two things: (1) Fertilization with human excrement; this is usually applied heavily to the kitchen garden. (2) Constant contamination of the farmers' shoes, and consequently the floors of the home, with human excrement. In addition, there is the water contamination, which, in Kentucky, runs to 80 per cent or more of the wells showing B. Coli.

Sincerely,

DAVID G. MILLER, JR., M.D.
Morgantown, Kentucky

August 6, 1947

Surgical Staff Meeting from Beth David Hospital

FREDERIC W. BANCROFT, M.D., Surgical Director

NEW YORK, NEW YORK

PHLEBOTHROMBOSIS

DR. BANCROFT: I should like to report one case which I think may be interesting to the obstetricians and gynecologists. It is an unusual case of phlebothrombosis which, I think, follows pregnancy.

Mrs. S. was delivered of a normal child ten days before I saw her. She was up on her sixth day. On the ninth day she had some cough. The next morning she had a sudden pain in her left chest and the x-ray showed fairly good evidence of what was either an infarct or a virus pneumonia. She had no tenderness or swelling in either thigh and no tenderness in either calf. She did have pin-point tenderness on each side at about McBurney's and corresponding points, which might be where her uterine veins entered into the iliac veins.

We operated on this patient on the tenth day following her delivery. Both femoral veins were isolated and incised between ligatures. They were in spasm but did not contain any thrombi. We did not think we would, but in passing the sucker up to about the junction of the iliac and hypogastric veins, we obtained very definite clots on both sides.

I think this case is interesting, particularly as a complication of obstetrics, because, if there is no swelling of tenderness of the veins, if there is a negative Homan's sign,* compression of the calf is negative, and if there is no edema, one is apt to forget that thrombosis may occur in the pelvic veins and then extend to the iliac vein, with a later retrograde thrombus of the femoral vein.

I had seen one similar case which interested me because of the time element. The patient had a caesarean section performed for a premature separation of the placenta in a seven-months' pregnancy. A live baby resulted, and the postoperative convalescence of the mother was extremely smooth. There was no postoperative elevation of temperature, and no complaint of abdominal or thigh pain. The patient left the hospital on the twelfth postoperative day. Three days later she complained of an acute attack of pain in the chest. She was readmitted to the hospital. Her temperature rose to 103° F. Three days after admission, x-ray of the left chest showed irregular consolidation. Her physician had gone over both legs and thighs carefully; there was no difference in their circumference by mensuration. There was no tenderness.

Ten days after her admission, the patient had a sudden swelling and pain in the left thigh. I was called to see her on the next day. Under local anesthesia the left femoral vein was exposed. A clot was removed. I did not feel, however, that I had reached the upper end of the clot because free bleeding was not encountered. It was a strange hospital and there was some difficulty in getting the proper kind of suction. Consequently, I did not insert a catheter high up in the iliac vein as I should have done, and I did not get as free bleeding as I wished. Her postoperative condition improved for about six days. Her temperature receded almost to normal, and she had no pain or swelling in the leg. However, eight days after thrombectomy, she had a sudden attack of pain in the right side of the chest, with elevation of the temperature. X-ray showed a cloudy right lung, with not as great consolidation as on the other side. Up to this time, there had been a question whether this was virus pneumonia followed by phlebothrombosis, or whether the initial infarct antedated the appearance of the phlebothrombosis by ten days.

Eight days after the second attack of pain in the chest, phlebothrombosis developed in the right thigh. This time, under spinal anesthesia, a clot was removed from the left femoral vein, followed by free bleeding. The patient, however, began to go into collapse during the administration of the low spinal anesthesia and her collapse continued after the removal of the clot. She was taken to her room in a serious condition. She died three days thereafter.

I quote from the autopsy report:

Lungs: The right lung is completely collapsed and attached to the chest wall by numerous strands of fibrin and purulent exudate. There is about 500 cc. of a fibropurulent fluid in the right pleural cavity. The right lung weighs

* Pain in calf on dorsiflexion of foot.

400 Gm. The left lung is adherent at the apex to the chest wall by old fibrous adhesions. About 100 cc. of thick purulent exudate is present in the left pleural cavity. The left lower lobe is completely collapsed. The left upper lobe is well aerated and pink in color. Examination of the branches of the pulmonary artery shows a large thrombus in the lumen of the right vessels with branches running to all of the lobes. This thrombus is yellow in color and adherent to the intimal layer of the vessel. On the left side, there is a similar-appearing thrombus in the lumen of the branch of the left pulmonary artery leading to the left lower lobe. There is no thrombus found in the lumen of the main pulmonary artery. No mediastinal node is found.

Uterus: The uterus is small and anteflexed. The operative wound in the anterior wall of the myometrium is well closed by chromic catgut sutures which are still present. Adherent to the anterior surface of the endometrium is some granular pink tissue which grossly resembles placental tissue. The tubes and ovaries are essentially normal.

The veins in the broad ligament of the right side are natural. On the left side, the vessels at the base of the broad ligament contain distinct, well-organized thrombotic tissue. The vena cava and both iliac veins are opened. The right vein contains some postmortem clot which is lying free in the lumen of the vessel. On the left side, however, the blood clot in the iliac vein is well organized, yellowish-pink in color, and adherent to the vessel wall. The thrombus runs up into the vena cava for a distance of 3 cm. At the upper end of this thrombus the blood clot is distinctly postmortem in nature. The branch of the hypogastric vein leading from the left iliac vessel is also thrombosed, as are those of the veins in the pelvis on the left side. In the region of the left femoral vein the thrombus in the lumen of the vessels appears relatively fresh but distinctly postmortem in character.

In that particular case, a ligation of the vena cava would probably have saved that woman's life if we had done it early, but I think we have got to realize that in obstetrical conditions we may have emboli thrown out before we have evidence of a retrograde thrombosis in the thigh.

DR. BREIDENBACH: Most emboli come from the legs, but still, when doing pelvic surgery or obstetrical surgery, conditions prevail which cause thrombosis in the pelvis first, in a certain per cent of these cases. I think one ought to go right in the vena cava rather than go after the legs, especially when there are signs in either leg to indicate that there is a thrombosis in the leg.

Recently following a hysterectomy, a patient was up and out of bed 24 hours after operation. On the third day she went to the bathroom, strained at stool, fainted, and had mild shock. Nothing was done. The next day she went to the bathroom again, again strained at stool and the same thing happened, but this time it was so severe that the patient collapsed completely and fell to the floor. She was brought back to the bed, and a cardiologist was called, who made a diagnosis of coronary thrombosis. He ordered an electrocardiogram. We decided she had a pulmonary embolus. There were no signs in the legs whatsoever.

I felt, since she had no signs in the leg and since the surgery had taken place in the pelvis, that very likely she had a thrombosis in the pelvis. Vena cava ligation was done and that was the end of the trouble.

DR. GOLDBERGER: How severe a procedure is that?

DR. BREIDENBACH: To ligate the vena cava is very simple.

DR. GOLDBERGER: Simple for the patient?

DR. BANCROFT: You make a right flank incision; then go retroperitoneal.

DR. BREIDENBACH: You can go transversely, through Petit's triangle. Cut through the external oblique. Push the peritoneum aside and do the same as with the lumbar sympathetics. To me, it is rather simple.

DR. GOLDBERGER: For the patient or the doctor?

DR. BREIDENBACH: For both.

DR. GOLDBERGER: Is it used generally?

DR. BREIDENBACH: Yes.

DR. GOLDBERGER: With pulmonary infarcts, etc.

DR. MALISOFF: How far down?

DR. BREIDENBACH: An inch below the renals.

DR. GOLDBERGER: Sometimes I wonder if the operation may not be as bad as the disease.

DR. BANCROFT: Quite a few of these ligations of the inferior vena cava have been done with relatively low mortality.

DR. ROTHENBERG: There is a book coming out now, published by the Second Auxiliary Surgeon Group, of all types of war injuries and they have a series of inferior vena cava ligations done transabdominally. I am not so sure how large the series is. Of course the surgeons were in there because of abdominal wounds, and they went into the abdomen and through the posterior peritoneum and ligated the vena cava below the renals. The mortality cannot be judged too accurately because the patient might have died from other than ligation of the vena cava. It can be done through the peritoneum.

DR. BANCROFT: I think the extraperitoneal approach is just as easy as the transverse, because you don't have to fight the organs.

DR. WARNER: What type of collateral circulation develops?

DR. BANCROFT: I have not done any, so I don't know, but the reports which I have seen, and Dr. Breidenbach can probably substantiate it, indicate that there is a moderate amount of swelling of the extremities but not very much.

DR. BREIDENBACH: That is correct. As a matter of

fact, I have ligated two vena cavae for the same purpose and neither patient had any edema at all.

DR. GOLDBERGER: What is the collateral circulation, do you know?

DR. BREIDENBACH: The lumbars and the deep epigastric.

DR. GORDON: I have seen a vena cava ligated recently. The patient developed the complication of paralytic ileus and marked distension of the abdomen, which must have been due to getting the sympathetics at the same time. It is possible to get the sympathetic chain there.

DR. BREIDENBACH: That should not be. Was it done retroperitoneally?

DR. GORDON: Yes.

DR. ROBBINS: At the Lahey Clinic they reviewed 50 cases of death from thrombophlebitis and they found many cases of pulmonary infarct without embolus in the veins. In doing them they found that one thing in common was a slight elevation of temperature the eighth or ninth day and felt many could have been saved if they had started the treatment at that time, so they use dicumarol and heparin if they find a slight elevation at that time.

DR. BREIDENBACH: My patient had dicumarol.

DOCTOR: Why should there be an embolus the day following ambulation?

DR. BANCROFT: Wait a minute! The embolus had occurred two days before. Dr. Breidenbach's patient was gotten out of bed the next day. It has been found that getting people out of bed has reduced but not eliminated embolism. The reason I brought that up here is that previously we felt that getting a patient out of bed meant having him sit up in a chair. Sitting up in a chair is about the worst position that you can have for obstruction of the distal veins. You have compression of the popliteal space. Poupart's is constricted where the veins go under it. It was brought out in San Francisco that if you are going to get patients out of bed, get them out and make them walk and then put them back in bed in the horizontal position. Have them sit in chairs as your last procedure.

PERFORATED PEPTIC ULCER—POSTOPERATIVE PNEUMONIA

DR. STANLEY GREENWALD (House Surgeon): I shall present a report of a patient with a perforated ulcer who developed postoperative pneumonia.

Here is the temperature chart of the patient. The patient came in with a three-hour history of perforation and was operated on within three hours of being in the hospital. His condition was relatively good postoperatively. On the second postoperative day he developed a left lobar pneumonia, received oxygen inhalation with increased penicillin intravenously. His condition is now very much better.

DR. STEIN: Increased penicillin?

DR. GREENWALD: We increased the penicillin from 30,000 to 50,000 every three hours.

DR. STEIN: Had he been getting penicillin?

DR. GREENWALD: He was getting it all along.

DR. STEIN: But he still developed pneumonia.

DR. GREENWALD: I went into the ward the night before and the windows were wide open and it was very cold in there. I am sure that precipitated it.

DR. STEIN: Could it be embolic?

DR. BREIDENBACH: This came on right after the operation?

DR. GREENWALD: Two days after operation.

DR. BREIDENBACH: Was there x-ray evidence of pneumonia?

DR. GREENWALD: There definitely was.

DR. ROTHENBERG: I think this case is interesting. It demonstrates something that we found out in the Army. All battle casualties had penicillin routinely. Despite this it was not uncommon, in the European theater anyhow, for patients on large steady doses of penicillin to develop postoperative pneumonias, the only difference being that it usually ran a mild course and that death from postoperative pneumonia was a very rare thing.

DR. BREIDENBACH: Don't you think that when pneumonic infiltrations come on this early, either in this or other cases, the etiology is an atelectasis due to a plug of mucus with subsequent pneumonitis, and that if there is obstruction of the bronchus you will develop some pneumonitis in spite of the penicillin? Just as soon as that plug is relieved and the lobe begins to drain, the penicillin will act and you get the pneumonic process subsiding. I think all these early postoperative reactions are definitely due to atelectasis followed by some pneumonitis.

DR. GREENWALD: In this case the x-ray revealed evidence of pulmonary congestion on the right side, so this may be secondary.

INTERN: Bacteriologic reports are showing that some organisms are becoming penicillin-fast and larger amounts of penicillin are required to combat these organisms than in the past. Just as was found with the sulfa drugs, many cases that previously would be treated with penicillin easily are now treated with difficulty.

DR. BREIDENBACH: I think the important factor is the mechanical one. If you have an abscess, penicillin

won't penetrate it and you get no result. Here the ineffectiveness is due to atelectasis or obstruction of a bronchus. Until that is loosened you get no drainage and the penicillin will do no good.

PERFORATED PEPTIC ULCER

DR. STANLEY H. GREENWALD: As usual, I would like to discuss the fatality first. This case was discussed at last week's conference. The patient, alleged to be 39 years old, had been on the Medical Service with symptoms of peptic ulcer and developed acute symptoms of perforation 36 hours before we saw him and before an operation was performed.

At operation the abdomen was found to be full of fluid. There were signs of active peritonitis. On the left side of the stomach there was a large perforation which was sutured. When the patient was brought to the operating room he was pulseless, the blood pressure was unascertainable. He was given blood on the table, plasma, stimulants, and returned successfully to his bed in the ward. However, in spite of all heroic measures—he received 2,000 cc. of blood 36 hours postoperatively, and 2 units of plasma and other fluids—the patient expired 36 hours after operation.

DR. LOUIS HAHN: This case was the one mentioned last week. In my own personal opinion it was futile to do any operation or to attempt any operation on this case. The patient was pulseless. Never once had we gotten a measurable blood pressure after the time we first saw him. I feel that in a situation as bad as that you might just as well save your efforts. If you cannot produce any reaction at all in the blood pressure or pulse by blood and plasma you are not likely to be able to save him by operative methods.

Our experience in the war has shown that the best way to handle a patient in shock is to try to relieve the shock with blood and plasma and then if you can get the blood pressure up around 65, 70, or 75 mm. of mercury operate and you may have some chance of saving him. If you cannot get the blood pressure up that way prior to operation, you are very likely to lose the patient on the table or very shortly thereafter.

In this particular case, I think possibly a little more vigorous treatment shortly after the perforation occurred was indicated. We did not see him until some time after the perforation, and, when we did see him and ordered treatment for the shock a little more vigorous attack with blood and plasma might have produced enough improvement so we could have gone in earlier.

The first time he was seen by the surgeons he had a walled-off affair and it was felt that with a Levine tube in the stomach any further outpouring through the perforation could be prevented and by treatment with blood and plasma we might get him over his shock. However, he was very refractory. He pulled out his Levine tube and probably at that time spread his localized peritonitis to a general peritonitis.

DR. S. GAINES: It is important to impress the interns with the importance of watching for perforation in any patient with an ulcer. This is the third case in about six months which I have seen perforate while in the hospital.

DR. HAHN: This case was on the Medical Service.

DR. GAINES: I am talking about the Medical and the Surgical Services. The first case I saw was when we had a meeting one night and I was just unofficially asked to see the patient. I said to the doctor in charge, "This patient looks as if he is perforating." That was about nine o'clock. At twelve o'clock midnight he had a terrific pain and at 1:30 A.M. the doctor called and at 2:00 A.M. we operated on the patient and he was saved.

There was another case, which I feel was neglected. A man was brought in with the diagnosis of acute appendicitis. I could find no evidence of appendicitis, and the man didn't remain under my treatment. I was told he vomited blood. It looked like an ulcer. The man unfortunately had a standing order for morphine for his pain. About four or five days later I was called in and he probably had had a perforation 24 or 36 hours before, because when I operated on him there was a tremendous amount of fibrin, which indicated a long standing perforation. That man died.

I feel it is very important in these cases to watch them very carefully because a patient like that should have been saved if the operation had been done immediately upon perforation.

To illustrate, when I was resident at Mt. Sinai Hospital, in making rounds and giving orders for one of the ulcer cases for operation the next morning, the man complained of severe abdominal pain. I made a diagnosis of perforation. I called up his doctor, who said, "We will watch him." I watched him for 15 minutes. Then I said, "Doctor, if you don't come down I refuse to take any responsibility." It is important to impress upon the medical man, or whoever is in charge, how important it is.

DR. STEIN: What is really the first symptom of perforation? You mentioned one case. You said that man was perforating and three hours after he developed a sharp pain. What did you observe there?

DR. GAINES: A very severe pain radiating posteriorly as a rule and beginning resistance of the deep abdominal wall.

DR. STEIN: Does the pain develop before the perforation or is it concomitant?

DR. GAINES: There is a certain amount of pain during perforation of the peritoneal coat of the stomach and irritation of the peritoneum.

DR. HAHN: Are there any other comments on this case?

DR. GRELNWALD: In Dr. Gudeman's absence, I would like to describe the postmortem findings. There was a large penetrating ulcer in the posterior wall of the stomach, penetrating into and adhering to the pancreas. It was the edge of the ulcer which perforated, the edge being on the lesser curvature, the main body being on the posterior wall, and it was about 2 cm. in diameter. The suturing had held. The belly was full of pus and there was evidence of increasing peritonitis.

DOCTOR: There were no signs indicating carcinoma?

DR. GRELNWALD: No, it was a typical ulcer, a very large one.

DR. ROTHLNBERG: I would like to say that it is just this posterior type of ulcer that will give the staggered *manifestations of perforation which this man displayed*, that is, it seemed to be a local perforation first, and then a generalized peritonitis. That occurs most frequently with this type of ulcer, an ulcer on the posterior wall.

Another thing which I think killed this man is the fact that he was in shock for as long a period of time as he was. When shock exists more than 16 to 24 hours it is completely irreversible. As. Dr. Hahn said earlier, he was beyond the stage where you could do any more for him, the state of shock had existed too long.

DOCTOR: In the use of that Levine tube, when you are aiming to empty the stomach, is that tube clamped at a certain point so as not to enter the duodenum, or is it just passed and drains whatever it may?

DR. HAHN: We have never had any trouble preventing the tube from entering the duodenum. Usually when we want to enter it we have trouble getting it through. It is not likely that it is going to enter the duodenum. Generally, you have to work with it. Even with the Miller-Abbott tube you have to work pretty hard to get it through the duodenum. You need never worry about the tube going in when you don't want it.

DOCTOR: From a theoretical point of view?

DR. HAHN: No, it was not clamped. The idea is not to put it in too far. We do not put the tube in far enough to reach the duodenum. We suck on it to keep the stomach empty so as to prevent any outpouring of additional fluid. That is the purpose of not putting it in too far.

PERFORATED PEPTIC ULCER

DR. STANLEY H. GREENWALD: Our first fatal case is that of a 54-year-old Puerto Rican janitor admitted from the emergency room. Twenty-four hours before admission, while he was stoking a furnace, he was seized with sudden severe pain in the right lower quadrant and collapsed. He had vomited several times in the past 24 hours. The history was very difficult to obtain due to language difficulty.

Physical examination on admission revealed a board-like abdomen with maximum tenderness in the right lower quadrant and obliteration of liver dullness. X-ray examination at the time showed air under the right diaphragm and possible fluid levels although the X-ray Department interpreted these linear markings as a fold of skin due to pressure of the casette against the patient's abdomen in the upright position. The air under the diaphragm was missed by me and several of the interns but was picked up by the attending surgeon as a pneumo*peritoneum due to the ruptured peptic ulcer and not* as a rupture of a gangrenous appendix, which was the diagnosis first offered.

The patient was taken immediately to the operating room, and under general anesthesia an upper right rectus incision was made and a prepyloric perforation approximately the size of a pea was found. There were about 1,500 cc. of thick, greenish, purulent fluid in the abdomen. This was suctioned off. There were signs of *peritonitis.*

The perforation was closed with two purse-string sutures and omentum placed over the area. The patient was returned to bed, given 1,000 cc. of blood postoperatively, but after 24 hours the temperature suddenly shot upward, and the patient expired in spite of all our vigorous treatment.

DOCTOR: How long after onset was he operated on?

DR. GREENWALD: About 30 hours.

DR. BRFIDENBACH: Does anybody else want to comment on this or interpret that x-ray as a fold of skin?

DR. ROTHENBERG: I think it is fluid.

DR. BREIDENBACH: I think it is fluid in the peritoneal cavity. You never see a skin fold. Skin won't show in an x-ray. Here is the fluid level and there is another level (indicating). I would interpret that as being fluid in the peritoneal cavity.

DR. ROTHENBERG: Yes.

DR. GREENWALD: There was fluid. This is the

prone position showing a great amount of distention. Is this the large bowel? (Indicating.)

DR. BREIDENBACH: That is the large bowel.

DR. ROTHENBERG: Dr. Fuchs operated on the patient but I can give you the details. I saw the patient for the first time in the operating room, and my interpretation of the x-ray was that he had a ruptured peptic ulcer. This conclusion was based on the crescentic area of air under the right leaf of the diaphragm (indicating), complete obliteration of liver dullness, and board-like rigidity. The picture was complicated. The man started with right lower quadrant pain and that is all he complained of; secondly, he had a very large umbilical hernia and a large left inguinal scrotal hernia, and I think some of the men felt that he might have strangulation of the bowel, but that was not the case. The small bowel and scrotum were distended and both herniae were easily reducible. As I say, I saw the man for the first time on the operating table. Closure without any technical difficulty was carried out.

As far as the postoperative course is concerned, the man was in shock immediately postoperatively. He was in shock pre-operatively too. He never rallied from it. I saw him the morning after operation. He had all of the outstanding characteristics of deep shock, was cold, clammy, and the blood pressure was not ascertainable. He received a total of 1,000 cc. of blood.

DR. GREENWALD: Plus 500 cc. of plasma.

DR. ROTHENBERG: 1,000 cc. of blood, 500 cc. of plasma, and an intravenous infusion, plus oxygen, but he never came out of shock. Naturally the important thing is that the man had had a perforation for some 30 hours prior to surgery.

DR. GREENWALD: I have to contradict the statement that the man was in shock pre-operatively.

DOCTOR: How long was he in the hospital before he was operated on?

DR. GREENWALD: Two hours. He was not actually in shock before he went to operation. That is why some of us were fooled by the picture. His blood pressure was 130/80 in the operating room.

DR. ROTHENBERG: When I saw him pre-operatively I immediately diagnosed it as shock.

DR. GREENWALD: We all thought if it was a perforated peptic ulcer, his cardiovascular signs would have been much more marked. After all, it was 24 to 26 hours old.

DR. BREIDENBACH: This case demonstrates the importance of a history in any abdominal lesion. You have no history here. The intern staff were unable to get a clear history due to language difficulty and the physical examination made some of them feel it was an acute appendicitis because he had a lot of signs and symptoms in the right lower quadrant, which we know occurs in perforated ulcer when the liquid seeps down in the right lumbar gutter. That is not an uncommon finding in peptic ulcer perforation. But the history is very important in making the diagnosis. There was no history because the patient couldn't speak English.

DOCTOR: Was there the usual board-like rigidity in this case?

DR. GREENWALD: Yes, there was.

DR. BREIDENBACH: The experienced visiting surgeon comes in and makes a diagnosis on physical signs. The intern must depend on physical signs and history, but of course the visiting surgeon by virtue of his greater experience can make a more accurate diagnosis without benefit of history. The interns should take this as an example. A diagnosis of ruptured appendix is not an uncommon finding in perforated ulcer, because of the seeping of the exudate into the right lower quadrant, and the history is very, very helpful. This man had herniae. There was a possibility he might have had strangulation with perforation of the gut in one of the herniae.

DOCTOR: They were easily reducible. That is what Dr. Rothenberg said.

DR. BREIDENBACH: They were reducible?

DR. ROTHENBERG: Very easily.

DR. BREIDENBACH: What are the findings on postmortem examination?

DR. GREENWALD: The postmortem findings show perforation of a pyloric ulcer. That was sealed completely. The omentum was still viable, and that is essentially all there was. The ulcer was about the size of a ten cent piece in the prepyloric region. Incidentally there were very few signs of peritonitis contrasted with the last perforated ulcer which we discussed here, which was taken over from the Medical Service where there were prominent signs of peritonitis.

The peritoneal cavity had a minimal amount of fluid. The difference in this case as compared to the previous case is that a stab wound was used for draining in this case. In the previous case no drainage was placed in the abdomen.

DR. BREIDENBACH: Did he have any pneumonic process?

DR. GREENWALD: I was told there was.

DOCTOR: Do you have the autopsy findings?

DOCTOR: Was there no peritonitis?

DR. ROTHENBERG: I don't think he lived long enough to develop any.

DR. BREIDENBACH: What was the cause of death?

DR. GREENWALD: Shock probably.

DOCTOR: Shock?

DR. GRLENWALD: Cardiovascular shock. What would be the usual cause of death in a case like this?

DR. BRLIDENBACH: Peritonitis. I would assume in this particular case he had enough in his belly to give him peritonitis.

DR. ROTHENBLRG: The man died in postoperative shock from the operative procedure.

DR. E. DONHEISER: Besides the 1,000 cc. of blood and plasma did he also get intravenous support?

DR. BRLIDLNBACH: Continuous intravenous infusion of saline and glucose?

DR. GRELNWALD: Yes.

DR. BRLIDENBACH: He was getting that all the time, besides blood and plasma.

DOCTOR: What did he need the blood for? That is the question. Why increase the cardiac work when the heart is knocked out? There was no hemorrhage there.

DR. BRLIDENBACH: Well, here is a man in shock, shock due to the loss of blood volume.

DOCTOR: Did you give fluid?

DR. BRLIDI NBACH: The best substitute, the best drug or the best medication for improving blood volume is blood.

DR. ROTHLNBERG: This man did not die because of being overloaded with fluid. He had no pulmonary edema. I had a feeling if he had another 2,000 or 3,000 cc. of blood he would have lived. As we all know, in these cases of shock I have given as many as seventeen units of blood successively and pulled a man through from deep shock. Of course, that is with hemorrhage, but 1,500 cc. of blood and plasma will not kill a man in shock by overloading his vascular system.

DOCTOR: He probably could have used 6,000–7,000 cc.

DR. BRLIDLNBACH: He got fluid continually intravenously.

DOCTOR: Did we do a postmortem examination of the splanchnic bed?

DR. MILTON HILPERN: Postmortem findings: Spontaneous perforation of peptic duodenal ulcer and acute suppurative peritonitis with no free fluid in the abdomen. Also, pulmonary edema and congestion, left inguinal hernia and left hydrocele.

DR. BRLIDENBACH: Overloading with fluids, blood and plasma is a common postoperative error and can easily lead to pulmonary edema and death. In this case by tally he did not receive enough fluid by vein to cause overloading. Clinically he had a mounting temperature indicating death was due to toxemia of a severe peritonitis.

STATEMENT OF THE OWNERSHIP, MANAGEMENT, CIRCULATION, ETC., REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946

of AMERICAN PRACTITIONER

published monthly at Philadelphia, Pa., for October, 1947

State of Pennsylvania

County of Philadelphia

ss.

Before me, a notary public in and for the State and county aforesaid, personally appeared J. Brooks Stewart, who, having been duly sworn according to law, deposes and says that he is the assistant managing editor of the AMERICAN PRACTITIONER and that the following is, to the best of his knowledge and belief, a true statement of the ownership, management, etc., of the aforesaid publication for the date shown in the above caption, required by the act of August 24, 1912, as amended by the acts of March 3, 1933, and July 2, 1946 (section 537, Postal Laws and Regulations), to wit:

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J. BROOKS STEWART

Sworn to and subscribed before me this 22d day of September, 1947.

HARRY J. BEARD
Notary Public

[SEAL]

My commission expires March 5, 1949.

Varicose veins and thrombophlebitis as well as their complications offer therapeutic problems in the practice of every physician. The author presents an excellent valuation of the untoward effects of varicose veins in the aged and the best methods of treatment. The subject of thrombophlebitis, its relationship to tumors and to recumbency as well as its treatment is covered clearly and in an interesting fashion.

Diseases of the Veins in Middle and Old Age*

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A consideration of diseases of the peripheral veins in older patients entails special details of pathogenesis and treatment, which are either not encountered in younger patients, or are changed in magnitude. An attempt will be made in this paper to bring together known details relating to these matters. They will be considered under the headings of varicose veins, and of thrombophlebitis.

VARICOSE VEINS

Clinical experience has taught the author that severe varices have their inception early in life, usually before the patient reaches the age of 30. Yet, because of previous trials with treatments, or because of neglect, the majority of patients present themselves for treatment during middle and old age.[1] Moreover, of 1,000 patients with varicose veins, previously reviewed from the Boston City Hospital, 37.5 per cent showed serious systemic disease.[1] Undoubtedly, a separate consideration of the older patients would have shown an even higher incidence of concurrent systemic disease, as well as arteriosclerosis of the limbs. Under these circumstances, it might well be asked whether it is wise to treat these patients in any way except by a local compressive bandage or stocking. The answer to this query is, (1) there are special reasons why the older patient should have his varices corrected, and (2) that using certain precautions, treatment is effective and well tolerated.

SPECIAL INDICATIONS FOR TREATMENT

The special indications for treatment present in older patients are threefold, and are mainly an intensification of the conditions present in youthful patients: (1) The constitutional circulatory effects of varicose veins; (2) the increase in severity of local lesions with advancing age, and the presence of complications; (3) the increased tendency to thrombophlebitis and pulmonary embolism.

The Constitutional Circulatory Effects of Varicose Veins. It was the author's early clinical experience to have older patients remark upon a feeling of improved well being, often with a lessening of effort dyspnea, following the obliterations of large varices. This subjective improvement was mentioned so often as to stimulate curiosity as to its cause. When a patient with varicose veins assumes the upright posture there is a sudden downward flow of a large quantity of blood from the femoral vein, past the incompetent valves of the saphenous vein, to fill the varices. The quantity of blood thus diverted from the returning flow may apparently be close to half a liter.[2, 3] It occurred to the author that this might be compensated for by a constant increase in total blood volume, which, as in patients with arteriovenous fistula, would be reflected in cardiac embarrassment. In 1937, K. J. Thomson and J. G. Gibson kindly offered to measure the blood volumes in several patients with varicose veins, but we were disappointed in obtaining equivocal results. It is possible that we failed to utilize subjects with sufficiently large varices, for in 1940, Lee and Freeman did find increased volume in patients with extraordinarily large venous angiomata.[2] In 1942, Chapman and Asmussen reported clear-cut evidence of the nature of the circulatory embarrassment.[3] They noted that patients with varicose veins often complained of dyspnea, dizziness, and precordial distress, on assuming the upright position. They write: "Asmussen, Christensen and Nielson have estimated that in normal persons standing still, 500 cc. of blood or even more accumulate in the legs. Consequent to such stagnation a smaller amount of blood is avail-

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This study was aided by a grant from the Charlton Fund.

able in the central veins emptying back into the heart; this decrease in venous return lessens the filling of the heart and results in a decrease in the cardiac output when standing; a fall in blood pressure under these conditions may be followed by a sudden increase in pulse rate. In our patients with varicose veins it is evident that an amount larger than 500 cc. accumulates in their veins during standing, and walking. Consequently, the same physiologic responses could be expected but in a greater order of magnitude." These expected responses were indeed found (Table 1). Moreover, the average blood volume of their patients was also somewhat higher than normal.

TABLE 1

Circulatory Functions on Passively Raising the Patient From the Recumbent to a 45° Upright Position
(From Chapman and Asmussen)

	7 Normal Subjects	12 Varicose Patients
Average age	45	48
Decline in cardiac out-put	5.0%	21.0%
Decline in Stroke Vol.	14.0%	39.0%
Decline in Syst. B.P.	0.3%	8.0%
Increase in pulse rate	15.0%	25.0%

We may deduce from these observations that if for no other reason, large varices in the elderly should be treated to remove a drag on the heart's function.

The Increase in Severity of Local Lesions with Advancing Age, and the Presence of Complications. Since the disorder has been progressing for many years in the older person, his limb is apt to show in heightened severity, the edema, fibrosis, and ulceration that the varices produce. These effects are still further increased in the presence of atherosclerosis. The discomfort of these changes are particularly annoying to a person no longer robust.

Several years ago de Takats spoke of "resting infection" in varicose veins, and the present author thought that this might be an additional reason for treating the varices. Further experience has led me to drop this view, for bacteriologic and clinical experience has failed to demonstrate convincingly that bacteria are frequently present in varicose veins, or that they play a pathogenic role.

Very rarely, epidermoid carcinoma may develop in a neglected varicose ulcer of long standing. The author has seen but one such case. Taylor, Nathanson, and Shaw reported 13 instances in a review of 430 cases of carcinoma of the extremities, a condition which itself is relatively uncommon.[4] The subject is well reviewed in a paper by Rubenfield.[5]

Moreover, the presence in the limb of two conditions common in older people, namely, arthritis of the knee joint, and atherosclerosis, constitute an additional indication for treatment. It has been the author's experience that the arthritis is often dramatically improved by treatment of the varices. Likewise, removing the burden of the varicose state is a definite aid to an atherosclerotic limb.

The Increased Tendency to Thrombosis and Pulmonary Embolism. Thrombophlebitis, of course, often occurs in varicose veins. In young active people this does not often lead to embolism. Contrariwise, this is a very serious condition in the older person, for he is apt to react to the painful process by confining himself to a chair or bed, thus setting the stage for propagation of the thrombus to the now stagnant deep vessels, with consequent great danger of pulmonary embolism.

Moreover, the older patient may often be confined to bed with his infirmities. It is under this condition that bland thrombosis of the deep veins is most apt to occur. The presence of varicose veins increases the likelihood of this condition supervening, for *thrombosis is especially apt to start in varicose veins* during prolonged recumbency. It then but remains for the process to extend to the deep veins, which it does very readily.

We may refer here to the statistics of Barker et al. who found that the presence of varices increased the chances of postoperative venous thrombosis almost threefold.[6] Furthermore, a previous thrombophlebitis of the superficial leg veins was especially hazardous. In 46 such patients subjected to operation in other parts of the body, there were 31 cases of postoperative pulmonary embolism, with 15 deaths. To quote Giertz and Crafoord: "One can hardly exaggerate the seriousness of performing, *without urgent necessity*, other operations on patients with large varices."[7]

Modifications of Treatment

The older patient does not tolerate well operative or sclerosing procedures in the distal portion of his lower limbs. There is the matter of pain, of possible nonhealing of the incision (particularly in an arteriosclerotic leg), and the danger of extension of a thrombosis, spontaneous, or induced by sclerosing solution, to the deep veins. It is important at the time of examination to determine whether there is only a reflux of blood to the varices from above downward in the saphenous, or whether in addition, there is a reflux outward through the communicating veins. In the first instance, the varices are ordinarily treated by di-

vision of the saphenous at the saphenofemoral junction. Additional surgery such as stripping of the saphenous is not well tolerated in older people. Furthermore, I think it extremely unwise to inject the saphenous from above at the time of operation, for it may lead to an extensive and intractable deep thrombophlebitis. Postoperative injections should be used sparingly. They should never be given if the patient is bedridden, for under these circumstances one courts propagation of the thrombus to the deep veins, and embolism. It is customary in younger patients with a suspected or demonstrated reflux through the communicating veins, to divide the communicating veins in the calf. This is a procedure too radical for the older patient, not because of the magnitude of the operation, but because of the patient's difficulty in readjusting his circulation postoperatively. In the older age group, one must be satisfied with division of the saphenous with or without limited postoperative injections, adding support if necessary in the form of compression bandages or elastic stockings. Arterial insufficiency of the limb is no contraindication to treatment if one limits one's procedures to the thigh and upper part of the leg.

It is unwise to start treatment of the varices just prior to an elective operation on some other part of the body for there is increased danger of deep thrombosis by an extension from the process in the superficial veins set off by the saphenous division or injections. Probably the safest procedure to follow if the patient is to have an operation elsewhere, is prophylactic division of the femoral vein below the entrance of the profunda, and division of the saphenous. This can usually be done at the same time as the elective operation.

THROMBOPHLEBITIS

In middle age and beyond, thrombophlebitis assumes some clinical forms not often seen in the young. It is useful to consider the disease separately when it occurs in the active patient, and when it occurs in the bedridden one.

Thrombophlebitis in Active Patients: Relation to Malignancy

As in younger people, the most common form of thrombophlebitis is that developing in varicose veins. This has already been considered. A more surprising event is its occurrence in previously normal veins in a patient who has been up and about, perhaps at work. In young persons such a process ordinarily arises as an extension from varices, from trauma, or as part of Buerger's disease, or of "recurrent idiopathic thrombosis." In older patients the usual cause is to be found in an attack of "recurrent idiopathic thrombosis," blood dyscrasia (particularly polycythemia), or malignancy.

Since the existence of malignancy is both serious and common, it behooves us to examine this matter in detail.

Thrombophlebitis in Direct Relation to the Tumor. *External Pressure from Tumors.* Venous occlusion when the vein lies within or against tumor masses, is of quite ordinary occurrence. It may be incidental to simple pressure of the tumor. This is most likely to occur in the apex of the thorax or in the pelvis. Here, the close association to the veins of regional lymphatics and nodes draining many viscera, as well as the rigidity of the confines of these regions is responsible for the high incidence. Venous obstruction by external pressure alone is perhaps most often seen in the upper thorax and base of the neck, related to tumors of lymphatic origin, and involving the superior vena cava, or the innominate or subclavian veins. Compression is usually followed by thrombosis especially if the tumor is carcinomatous, as is more often the case in the pelvis.

Malignant Invasion of the Veins. It is worth reading the excellent accounts of Ewing,[8] and Willis,[9] of the involvement of veins by external malignancy. Willis writes: "Infiltrating tumors frequently invade the walls of veins, penetrate the lumen, and proliferate intravascularly. Certain classes of tumours, e.g. renal carcinoma, are notorious for their behaviour in this way, and may extend continuously along venous channels for great distances. It is, however, important to recognize that venous invasion is not peculiar to any particular class of neoplasm, but is exhibited in greater or lesser degree by almost all types of malignant growth."

In support of this thesis, Willis cites gross or microscopic invasion of veins in 29 per cent of 323 autopsies for malignant disease of all types he has reviewed. Among later reports may be mentioned the finding of 54 per cent vein involvement in 509 cases of hypernephroma by McDonald and Priestley,[10] and 41 per cent in 162 cases of cancer of the colon and rectum by Grinnell.[11] The vessels involved are both the veins traversing the tumor, as well as veins in the vicinity of primary or secondary tumor masses.

Thin-walled veins may be penetrated by mechanical pressure of the tumor, or more usually, there is infiltrative growth via tissue clefts in the adventitia, perivascular lymphatics and lymphatics of the vein wall, or by the vaso vasora. Thrombosis of the vein

is apt to occur as soon as the tumor reaches the adventitia (Fig. 1), but may be delayed until the tumor has actually reached the lumen.

The significance of venous penetration for the body as a whole, is its importance as a mechanism for metastasis. The tumors may grow for long distances intravascularly, but more important is the tendency of the tumor cells to break off and form emboli. There has been ample demonstration that this happens, but there is considerable controversy over the mechanism of transport of tumor emboli to distant parts of the body.[12] Especially important in this connection is the apparent role of the vertebral "system" of veins as presented by Batson in 1940.[13] This



FIG. 1. Thrombosis (Th) in an iliac vein secondary to carcinomatous infiltration (Ca) of the adventitial lymphatics. The carcinoma was primary in the lung, with secondary growth in the pelvic organs and lymphatics.

system includes the vertically disposed and connected plexuses of intra- and extravertebral veins (Fig. 2). These extend along the entire column, communicate with the intracranial venous sinuses above, and along their length, with the veins of the neck, the chest and abdominal wall (and thus with those of the lung, breast, kidney), the pelvis (rectum, uterus, ovary, prostate), and the veins of the upper and lower extremities. Batson has indicated that during forced expiration, as in coughing, defecation, etc., blood may flow from the veins of these organs, not to the caval system, but rather to the vertebral system, and within the latter from one level to another, often in a retrograde direction. In this way cancer emboli may be carried from their origin to a quite distant vein and place, without being carried through the caval system and pulmonary circuit.

It is not often that venous involvement becomes clinically recognizable except in the extremities. The axillary or subclavian vein may be affected by a cancer of the breast, but usually only after the primary lesion has attracted attention. Rather uncommonly, the superior vena cava or its tributaries are compressed or thrombosed by an intrathoracic lymphoma, or carcinoma. The author has seen instances in which edema and pain in the upper extremity have been the first symptoms for which the patient sought relief.

Before mentioning the clinical manifestations of peripheral vein involvement, it may be well to mention that malignant infiltration of the lymphatics ordinarily precedes that of the veins. Edema of purely lymphatic origin may therefore be seen in such limbs both prior to venous compression or thrombosis, and later, augmenting the edema incident to the venous obstruction.

Symptoms arising long after the malignancy has been discovered are quite commonplace, but more interesting is the history when the patient has been active and ignorant of the presence of malignancy. It is ordinarily as follows: The primary symptom was edema of the extremity, developing slowly, starting at the ankle, increasing, and rising higher up the limb over several days or weeks. In some patients severe pain radiating down the limb suggests the involvement of the vertebrae and spinal nerves that may coexist. Examination shows a pale, cold edema, without cyanosis, evenly distributed about the circumference of the leg. So far, the situation is characteristic of lymphatic block. Should thrombosis of the femoral or iliac vein supervene, there will be a sudden increase in edema, to the mid-thigh, if the femoral is involved, or to the level of the groin, if the external iliac is occluded. Edema extending to the lower buttock indicates blockage of the common iliac vein. Discomfort is felt along the course of the femoral vein, and in the sacral region if the common iliac is involved. The limb is now cyanotic.

The author has never seen an instance of pulmonary embolism from thrombosis developing in these veins while the patient is active. The keynote of management is to search for the etiologic lesion, treating the limb with a supportive bandage or stocking, adding paravertebral sympathetic block if there is much pain or cyanosis.

Thrombophlebitis Distant from the Tumor. Quite aside from the "marantic" thrombi seen in the terminal stages of malignancy, and discussed below, patients with visceral carcinoma may show spontaneous thromboses in one or more veins, superficial or deep, distant from the tumor proper. As mentioned above, a vein

may be involved by tumor carried from distant organs, but this is not the alleged mechanism in the group under present discussion. The few pathologic examinations made in these cases have not shown malignant invasion of the vessel, and there is rather a feeling that the thrombosis is caused by a coagulative tendency induced by the tumor.[14]

Such peripheral thrombi may occur months before the diagnosis of visceral carcinoma becomes obvious. the first sign of cancer of the stomach are recorded by Welch,[12] Thomson,[17] Sproul,[14] and Cooper and Barker.[18] On the basis of extensive autopsy review, Sproul indicates that the thrombosis, especially if multiple, is even more indicative of carcinoma in or near the body or tail of the pancreas, and this view is shared by Cooper and Barker. In both reports, too, carcinoma of the lung is also mentioned as associated with peripheral venous thrombosis.

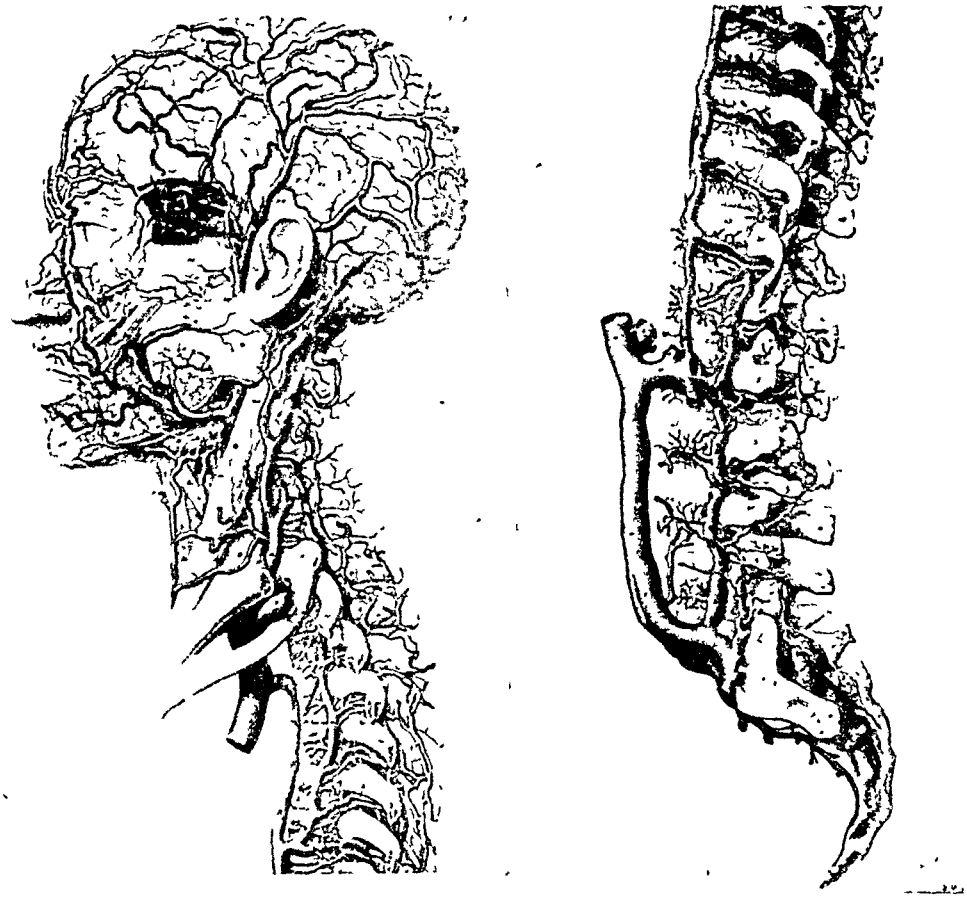


FIG. 2. The vertebral veins: a left lateral view of their extravertebral portions, from Breschet. The hemi-azygos vein is shown originating in the renal. The ascending lumbar vein is large, and communicates with both the common iliac and renal veins. (Breschet, G.: Recherches anatomiques, physiologiques et pathologiques sur le systeme veineux, Paris, Rouen, 1830)

This was apparently first noticed by Trousseau in 1862, who said: "When you are undecided about the nature of a disease of the stomach, when you hesitate between a chronic gastritis, a simple ulcer, or a carcinoma, a phlegmasia alba dolens occurring in the leg or arm will put an end to your indecision, and you will be able to assert positively, that a cancer is present." [15] This was the unhappy sequence of events in Trousseau himself, who died of a cancer of the stomach.[16]

Similar cases indicating peripheral thrombosis as

CASE REPORT: C. H. W. Pratt Diagnostic Hospital, No. 20057.

This 54-year-old farmer was admitted for study of a migrating thrombophlebitis. He had been well until seven months before admission, when he developed pain in the epigastrium and across the chest, worse at the time of hunger. This was associated with some nausea. There was generalized weakness and progressive weight loss. The pain was much improved after four months, but "gaseous" distress after meals was prominent. Three months before admission, he devel-

oped multiple, migrating thrombophlebitis, lasting about three weeks at each site. In this space of time, he had three attacks in each leg, two in each arm, and one in the left posterior cervical triangle.

On examination, the man appeared somewhat emaciated. There was a subsiding acute thrombophlebitis in the superficial veins of the left cubital fossa. The left leg was edematous to the buttock with apparent thrombophlebitis of the common iliac vein, the deep veins of the calf, and superficial and deep veins at the groin. Previously involved veins appeared as non-tender cords. The rest of the patient's examination revealed no pronounced pathology except for a small mass in the left lower neck, a moderate hypochromic anemia, and a moderate hydronephrosis of the left kidney with calculi in the kidney and lower ureter.

The gastro-intestinal x-ray series was normal. The pancreatic function test showed an increase in urine diastase—495 units. A biopsy of the mass of the neck was done by Dr. C. S. Welch, and reported as follows by Drs. H. Wood and J. M. Edelstein: "Well differentiated, mucus secreting adenocarcinoma, metastatic,—source probably gastro-intestinal tract."

The final diagnosis was adenocarcinoma, probably of the body of the pancreas, and migratory thrombophlebitis, secondary to that lesion.

Thrombophlebitis Developing During Prolonged Recumbency

Thrombophlebitis of the lower extremity may complicate or follow any condition which causes the patient, particularly an older patient, to remain in bed for prolonged periods. These conditions fall into three common groups: acute infectious disease, trauma, and operations.

Typhoid fever was formerly the most notorious infection in this regard, but with the present rarity of this disease, pneumonia and rheumatic fever are now, in my experience, the commonest. There seems to be a general lack of appreciation of the frequency with which trauma, expressed as severe sprains, contusions or fractures, causes thrombophlebitis. Most textbooks on fractures dismiss this complication as a rarity. The true importance of trauma as a cause is emphasized in several reports. Thus McCartney found that of 283 autopsies for pulmonary embolism 61 were secondary to trauma, mainly fractures of the femur or tibia.[19] The proportion is higher in medical examiner's cases. Vance found that 60 of 90 autopsied cases of pulmonary embolism were secondary to trauma,[20] and Martland found the same relationship in 55 of 86 cases.[21] The frequency of pulmonary embolism after hip fractures has recently been emphasized by Golodner et al.[22]

Turning to thrombophlebitis following operation, we find that this is the commonest form encountered, and since it differs in no essential respect from that following infections or trauma, we may now consider this condition in some detail.

Postoperative Thrombophlebitis. It has been amply demonstrated that this complication usually first arises in the deep veins of the calf, and may ascend to the femoral or iliac veins or to the vena cava. Whether or not signs of inflammation are present, bacteria cannot be demonstrated in the thrombus with any consistency, and we must look on the process as a bland one.[23] This is quite apart from frankly purulent thrombophlebitis arising in the vicinity of sepsis.

That postoperative venous thrombosis is especially prone to develop in older patients is emphasized by statistics from the Mayo Clinic.[6] Thus of 1,665 cases of postoperative venous thrombosis, 84 per cent of the cases in men, and 75 per cent in women arose in patients over 40. Undoubtedly this is due in part to the increased incidence of some operations peculiarly apt to give this complication, for example: gynecologic operations, prostatectomy, and repair of hernia. Moreover, the exaggerated immobility of the older patient may play a part in this high incidence.

But we must further take into account certain conditions, increasingly present in older people, which are generally thought to increase the hazard of thrombosis. This is borne out in the analysis quoted above.[6] Thus, examining the cases of abdominal hysterectomy, it was found that patients with certain concurrent diseases showed the following incidence of postoperative thrombosis:

Cardiac disease	7.2 per cent
Peripheral vein disease	5.6
Blood disease	9.3
Carcinoma	4.7
Severe infections	5.8

And in distinction to this—

No predisposing condition	1.9 per cent

Likewise, *once a deep thrombophlebitis is established,* the danger of embolism and death increases with age. This is indicated by the analysis of Welch and Faxon from the Massachusetts General Hospital.[24] The incidence of one or more pulmonary infarcts increased only moderately with age, being

28 per cent in patients under 50
31 per cent in patients between the ages of 50 to 70
40 per cent in patients 70 and over

The incidence of *fatal pulmonary embolism,* however, increased sharply with advancing age. It was

4 per cent of all patients
"Extremely low" in patients under 50
7 per cent in patients between the ages of 50 to 70
20 per cent in patients 70 and over

The avoidance of immobility is basic in the prevention of thrombophlebitis. This includes all forms of exercise, deep breathing, frequent turning, and passive motion in the immediate postoperative hours; and active exercise afterwards. A significant endorsement of this idea comes from the autopsy statistics of Hunter and his associates,[25] who found an incidence of thrombosis in the leg veins of 53 per cent in nonexercised patients, but only 18 per cent in those who had been exercised. Early ambulation, which is decidedly useful from many viewpoints, has so far failed to lower the incidence of thrombosis.[26]

Several clinics are now using dicumarol as a postoperative routine. It is too early to say whether this is a good plan to adopt universally. In the author's opinion, however, a history of previous thrombophlebitis in either the superficial or deep veins necessitates the postoperative use of dicumarol, or a prophylactic division of both femoral veins at the time of operation. It must be borne in mind that dicumarol is contraindicated in liver disease, and that its use must be closely checked with the prothrombin time.

Once a postoperative thrombosis is established, it would seem that division of the main venous trunk is preferable if it can be easily performed above the thrombus. The following working rule has proved to be practical in instances of deep-vein thrombosis: If the process is still limited to the calf or lower thigh, divide the femoral vein. The femoral vein of the apparently sound limb should also be divided for it often harbors a silent thrombus.

If the process has extended above the femoral vein, and there has been no pulmonary embolus, dicumarol may be used in place of iliac or vena caval ligation, using heparin for the first 24 to 48 hours, till the dicumarol exerts its effect. However, in all but exceedingly sick patients, division of the iliac vein or vena cava should be done if the patient has had an embolus.

"Marantic" or Terminal Thrombosis. In old, bedridden patients, dying of advanced carcinoma, tuberculosis, or heart disease, one finds the remarkably multiple thrombosis of major veins described by Welch. Circulatory stasis is prominent in these patients, and the term thrombosis, rather than thrombophlebitis is particularly applicable here. One finds enormous blood clots in the large veins—the venae cavae, the innominate, subclavian and iliac veins, and occasionally in the heart chambers. These thrombi may exist a variable number of days before death, and usually give no external evidence of their presence. They are terminal in more ways than one, for they ordinarily give rise to fatal pulmonary embolism. While the issue of life or death of the patient has usually been settled prior to their occurrence, this does not always hold true. Especially in cardiac decompensation the patient's condition may still be reversible, and the thrombosis deserves treatment along the principles laid down for postoperative thrombophlebitis.

SUMMARY

As patients grow older, there is greater importance in the proper therapy of varicose veins. These patients are progressively less able to compensate for the strain on the heart's function consequent on the shunting of blood into the varices. With increased duration of the varicose process, there is a proportional increase in severity of the edema, fibrosis, and ulceration of the extremity. The presence of varices heightens the severity of arthritis of the knees, and puts an additional burden on an atherosclerotic limb. Likewise it leads to an increase in the incidence of thrombosis and pulmonary embolism.

Varicose veins in older people may be safely treated by division of the saphenous vein at the groin. Surgical procedures below the knee are not well tolerated in older people. Because of the dangers of thrombosis and embolism, treatment should not be instituted if within a few weeks a surgical operation is contemplated for some other reason. In such cases, a prophylactic division of the femoral and saphenous veins may be done at the time of the operation in question.

Thrombophlebitis occurring during the active life of the older patient bears a particular relation to malignancy. It may be secondary to external pressure of the tumor or to malignant invasion of the vein, especially in the apex of the thorax, or in the pelvis. "Venous invasion is exhibited in greater or lesser degree by almost all types of malignant growth" (Willis). The invasion leads to tumor emboli and metastasis. The problem in this form of thrombophlebitis is primarily one of recognition of the tumor. The author has not seen ordinary pulmonary embolism from such a process.

Thrombophlebitis may develop distant from the tumor in superficial or deep veins. It is said to indicate particularly, the presence of carcinoma in pancreas, stomach, or lung.

Thrombophlebitis, particularly of the lower extremities, may occur during prolonged recumbency, for any reason. Pneumonia and rheumatic fever are the commonest infections in this respect. Trauma to the lower extremities, with or without fracture, is prone to give thrombophlebitis and pulmonary embolism. In middle and old age there is increased chance for postoperative thrombophlebitis. This is due in part to the increased incidence of diseases of the heart, peripheral veins, blood, and of carcinoma. Fatal pulmonary embolism is much more common in older than in younger patients. Either dicumarol, or division of the femoral vein should be used as prophylaxis in the patient with evident predisposition. At present, division of the femoral vein is the treatment of choice if the thrombophlebitis is established.

In the terminal stages of cardiac or malignant disease, marantic thrombi are apt to form in the large veins and cardiac chambers. They commonly give rise to fatal pulmonary embolism.

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Dysentery is commonly encountered in practice. Accurate etiologic diagnosis, in the chronic forms especially, is imperative for the rational use of the newer chemotherapeutic agents. The place of the clinical picture and the laboratory aids in diagnosis are weighed by the author as well as the indications for the use of the various therapeutic substances.

The Dysenteries*

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Dysentery is usually defined as a disease syndrome characterized primarily by the occurrence of bloody diarrhea. However, the dysenteries may be caused by a wide variety of agents and, furthermore, in some conditions that are usually considered dysenteric disorders the most disturbing and prominent feature may not be bloody diarrhea. Another fact that must be considered is that with the advent of specific chemotherapeutic substances rational and proper treatment is largely based on determining the correct etiologic agent. For this information the clinician is dependent on laboratory studies, particularly the microscopic examination of fresh stools and their culture on properly selected media. However, the patient's history, as well as certain specific clinical features of each form of dysentery are frequently of value in providing a clue to the etiology. The dysenteries may be broadly classified as those due to (1) food poisoning, (2) bacterial infections of the lower gastro-intestinal tract (bacillary dysentery), and (3) amebiasis. In discussing these disorders the rare and uncommon types will be purposely omitted.

FOOD POISONING

Food poisoning is a symptom complex usually characterized by acute gastro-enteritis with the sudden onset of vomiting or diarrhea or both. Abdominal pain commonly occurs and there may be fever, prostration and even shock. The causes of food poisoning have been classified by Dack[1] as (1) chemical, (2) plant, and (3) bacterial. The first two of these are relatively unimportant and need not be discussed in detail. The bacterial type, however, is widespread and it has been stated[2] that every person in North America has bacterial food poisoning at least once in his lifetime. The important bacterial food poisonings are classified in Table 1.

TABLE 1

Bacterial Food Poisoning

DISEASE	AGENT	TYPE	SYMPTOMS	ONSET
Staphylococcus food poisoning	Enterotoxin of staphylococci	Intoxication	Vomiting Abdominal cramps Nausea Diarrhea	1–6 hours
Salmonella food poisoning	S. enteriditis S. typhimurium S. choleraesius and others	Infection	Abdominal pain Diarrhea Chills Fever Vomiting	7–72 hours
Streptococcus food poisoning	Alpha streptococci	Infection	Nausea Colic Diarrhea	5–18 hours
Botulism	Clostridium botulinum	Intoxication	Dysphagia Diplopia Alphonia Respiratory paralysis	18 hours to 3–4 days

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The most frequent type of bacterial food poisoning in the United States is that due to the enterotoxin produced by the growth of certain staphylococci. This disease is a true intoxication and is not primarily an intestinal infection. The foods are usually contaminated by infected humans. Droplet infection from foci in the upper respiratory tract or direct transfer of infected exudate from cutaneous lesions are the chief modes of contamination. Milk, custards, pastries, sandwiches, salads, ham, tongue and similar meats are the foods most commonly involved. Symptoms usually appear three hours (one to six) after eating. Malaise and nausea, followed by vomiting, retching and abdominal cramps appear abruptly. Diarrhea may or may not be a feature. In a few cases prostration and shock may follow. The diagnostic features are (1) the short incubation period, and (2) the history of eating a suspected food with the additional story that a majority of those who ingested the food became ill. Culture of the suspected food will show several hundred million staphylococci per gram and the enterotoxin may be demonstrated.[2]

This disease is of short duration and treatment is symptomatic. Solid foods should be withheld during the acute phase, but liquids must be given in abundance. In the occasional case severe dehydration may require parenteral fluids, particularly saline solution. Prophylaxis is important and should include avoidance of contamination of food by infected food handlers and adequate refrigeration of the food. Continuous refrigeration of food (4 to 6° C.) will prevent the formation of enterotoxin in contaminated food, but it should be remembered that although heat (cooking) will destroy the staphylococci present in contaminated food, it will not destroy the enterotoxin once it is formed.

Food poisoning due to the Salmonella group of organisms is a true bacterial infection. At the present time there are 164 strains or types of Salmonella.[3] About 25 per cent of these strains have been isolated from human infections, the remainder being of various animal or avian sources.[4] The most commonly encountered strains and their hosts are listed in Table 2. Dack [1] divides these organisms into two groups on the basis of the clinical syndrome that is produced: (1) Organisms such as S. paratyphi (formerly called paratyphoid A) which infect man only and cause a mild disease resembling typhoid fever; and (2) organisms that primarily infect animals and may cause a typhoid-like disease, but which also produce a food-poisoning syndrome in man when ingested in large numbers. This type of food poisoning occurs as the result of the ingestion of contaminated food. The sources of this contamination are meat from infected animals, food contaminated by the urine or feces of infected rodents (rats or mice) and food contaminated by human beings during a temporary carrier state following infection.[5] The foods most commonly involved are made-up meats (S. enteriditis), sausage (S. choleraesius), salads, especially chicken salad (S. typhimurium) and smoked fish.

TABLE 2

Important Salmonella and Hosts

SALMONELLA SPECIES	HOST
S. paratyphi A.	Man
S. schottmuelleri (S. paratyphi B)	Man
S. choleraesius (S. suipestifer)	Hogs
S. enteriditis (Gaertner's bacillus)	Cattle
S. typhimurium (S. aertrycke)	Mice, rats, man

After a long incubation period of 6 to 70 hours there is a violent, explosive diarrhea associated with severe abdominal pain and tenesmus. There may be an initial chill followed by fever. Nausea, vomiting, muscular weakness, faintness and thirst may occur. Rarely there is septicemia with metastatic foci of infection, particularly in children.[6, 7] The stool culture will be strongly positive during the early acute stage. The diagnostic clinical features are (1) the long incubation period and (2) the fact that the majority of individuals ingesting the contaminated food became ill. In contrast to Staphylococci food poisoning with a short incubation period and in which vomiting tends to be the dominant feature, in Salmonella food poisoning vomiting is less common, the main feature being diarrhea. On the other hand, aside from the findings on stool culture, it may be impossible to clinically differentiate salmonellosis from bacillary dysentery or shigellosis. In cases where there is a high prolonged fever out of proportion to the degree of diarrhea a Solmonella septicemia should be suspected and a blood culture be obtained.

Treatment of Salmonella food poisoning is both symptomatic and chemotherapeutic. Symptomatic therapy includes use of liquid or soft, low roughage diet during the acute phase, maintenance of fluid balance, employing parenteral saline if necessary in the severely dehydrated cases, and mild sedation. Strong purgation with magnesium sulfate or castor oil is often recommended, but we feel that this is usually not indicated since it merely adds to the patient's discomfort and accomplishes very little. Specific chemotherapy is not yet available for the Salmonella organisms in spite of the fact that there have been many laboratory studies relative to sera, vaccines and bacteriophage in a variety of Salmonella

infections.[5] Likewise, there is still no good evidence to indicate that any of the sulfonamides or antibiotics † are effective either in shortening the clinical course of Salmonella infection or causing stool or blood cultures to become negative.[6] However, it is our feeling that in the case that does not respond promptly to symptomatic therapy or in which there appears to be a carrier state one of the local acting sulfonamides such as sulfasuxidine or sulfathalidine should be employed. The latter drug particularly in doses of three to four grams daily is advised. A further trial of streptomycin seems reasonable in those cases with septicemia.[6]

The other forms of food poisoning listed in Table 2 are relatively uncommon. Inadequate home canning is the usual source of botulism in the United States. Although comparatively rare, botulism when it does occur is a serious intoxication producing dysphagia, diploplia, aphasia and respiratory paralysis. Streptococcus food poisoning is a true bacterial enteritis and no enterotoxin is produced.[1] Four hours (3 to 18) after eating, colic, diarrhea, nausea, and vomiting occur. Rapid recovery ensues (24 hours). Epidemiology and prophylaxis are the same as for staphylococcus poisoning.

BACILLARY DYSENTERY

Bacillary dysentery is an infectious disease caused by several members of the genus Shigella, the dysentery bacilli. There are many varieties of Shigella, but for our purposes they may be broadly classified into three main groups:

1. Sh. dysenteriae, the Shiga bacillus, and Sh. ambigua, the Schmitz bacillus.
2. Sh. paradysenteriae, the Flexner, Boyd types.
3. Sh. sonnei, the Sonne, Duval bacillus.

Each of these groups produces a generally characteristic clinical picture. The Shiga bacillus produces severe epidemics and is most common in the tropics and subtropics. It produces a powerful exotoxin. The Flexner organism is the most common in the United States and causes a milder, less severe form of the disease. It produces no exotoxin. Infection with this organism less commonly results in chronic dysentery. The Sonne bacillus also causes a less severe dysentery, but is more resistant to therapy. In addition to the difference in the clinical picture of the various Shigella, there is also an important difference in regard to the geographical distribution. It has been shown that Sh. paradysenteriae (Flexner) is generally the predominant cause of endemic dysentery in the United States.[9] However, in some areas Sh. sonnei seems more important, particularly in the southeast where this organism has been found more commonly than all other types combined.[10] A recent survey [11] confirms these findings and indicates the rarity of the Sh. dysenteriae (Shiga) in the United States.

Bacillary dysentery is spread by the contamination of food and water by the feces of infected individuals. When the disease is prevalent carriers are not uncommon. In the case of the Flexner organisms approximately seven per cent of the cases of infection with this type become carriers,[12] and thus the carrier problem becomes very important in the spread of bacillary dysentery. In addition to the fecal pollution of the water supply, transmission is accomplished also by contamination of food by infected food handlers and by the transfer of the organisms by house flies. Prevention then depends on good sanitation which implies (1) avoidance of contamination of water and food, (2) diagnosis, isolation and treatment of contagious carriers, and (3) the careful and frequent examination of food handlers (stool culture) and the food and water supplies.

The clinical manifestations of bacillary dysentery vary from a mild diarrhea to a severe cholera-like disease. Variations in the severity of bacillary dysentery have led to the clinical classification of the disease by Manson-Bahr [13] as (1) mild or catarrhal, (2) acute, (3) fulminating, (4) relapsing, and (5) chronic. In the usual infection with the Flexner strain (more common than Shiga in the United States) there is a 12 to 48 hour prodromal period characterized by malaise, headache, anorexia, nausea, low-grade fever and watery diarrhea. There is then a sudden rise in temperature with abdominal cramps, tenesmus and frequent rectal discharges of bloody mucus. Later the stools become purulent. Palpation of the abdomen reveals a tender, spastic sigmoid colon and ileum. The severe diarrhea may lead to dehydration and marked inanition. In the second week symptoms gradually subside. There are many atypical clinical forms of which the appendicular one is quite important. There is neusea, headache and a slight fever associated with pain in the right lower quadrant. Usually this can be differentiated from appendicitis by the absence of leukocytosis and true abdominal rigidity. Furthermore, in bacillary dysentery there is

† We have recently observed an outbreak of Salmonella schottmuelleri enteritis on the tuberculosis unit in the University Hospital. A special high caloric formula was the source of the infection. Stool cultures were positive in seven cases, and interestingly enough, three of these cases were under therapy with streptomycin at the time the stool cultures became positive. This therapy was continued during the acute enteritis. There was no difference in the duration or severity of the clinical course or in the time necessary for the stool cultures to become negative in the streptomycin group as compared to the four cases receiving symptomatic and supportive therapy alone.

a tendency for the pain in the right lower quadrant to shift with changes in the patient's position. Occasionally, there are instances in which the prodromal period resembles pneumonia or meningitis. In some patients there is severe constipation rather than diarrhea after the prodrome. Some cases may be afebrile and asymptomatic. In Shiga infections, which generally are of the fulminating type, the disease is more severe with marked toxemia. Furthermore, it is more prolonged, the mortality rate is higher and there is a greater tendency for relapses to occur. Sonne infections are generally mild. There may be only malaise with frequent green, mucous stools. In the Sonne type there is a greater tendency for a chronic dysentery to persist.

Chronic bacillary dysentery results from prolonged infection of the colon with the Shigella, lasting over several months or years. There may be periods of apparent quiescence with frequent recurrent episodes of acute dysentery. Eventually the persistent and chronic infection leads to diffuse cicatrizing, ulcerative, polypoid lesions of the large bowel and occasionally of the small intestine. Under these circumstances x-ray examination of the colon reveals anatomic deformities that may be indistinguishable from those seen in idiopathic chronic ulcerative colitis. The nutrition and general physical condition of the patient suffer and there is gradual loss of weight and chronic fatigue. Because of these chronic cases it has been suggested that all cases of chronic ulcerative colitis are the result of chronic bacillary dysentery,[12] but this view is not generally accepted. Aside from this chronic form which may be considered a complication of acute bacillary dysentery the other important and common complication is that of arthritis. This may be mono- or polyarticular and usually occurs in Shiga infections after the acute stage is over.

Definitive diagnosis of bacillary dysentery is based on the isolation of Shigella by culture of fresh stools or material directly wiped from the rectal or colonic mucosa during sigmoidoscopy. The diagnosis may be made presumptively by the gross and microscopic examination of fresh stools. Grossly the stool is a homogeneous sticky mixture of blood, pus and mucus. This rectal discharge is comparatively scant and resembles "red currant jelly." Microscopically the rectal discharge shows many well-preserved pus cells with intact nuclei. There are scattered red cells and there are many degenerating epithelial cells. Large nonmotile macrophages containing red and white cells are present and must not be mistaken for amebae. The marked cellular content of the rectal discharge is the characteristic feature of bacillary dysentery. Sigmoidoscopy is often of help in the diagnosis of a suspected case. The typical picture is that of a diffuse hyperemia of the rectal mucosa. Mild trauma causes bleeding and submucosal hemorrhages are common. There is blood stained mucus in the lumen. Very superficial ragged ulcers may be present. Characteristic cream-colored miliary abscesses pinpoint to pinhead in size are seen. Agglutination tests for Shigella are not of much help in the diagnosis of the acute case since they do not become positive until the second week of the disease. In the more prolonged cases, however, a rising titer in agglutination is important. Initial positive titers of 1:150 for Flexner organisms, 1:40 for Shiga and 1:100 for Sonne are suggestive of infection.

Treatment of bacillary dysentery includes (1) symptomatic and supportive therapy, (2) chemotherapy, and (3) serum therapy. Supportive treatment consists of bed rest, mild sedation (e.g., phenobarbital ½ grain q.i.d.), heat to the abdomen for pain, and adequate fluid intake. Liquids should be given in abundance (at least three liters per day) to avoid dehydration. The diet may be liquid or soft, but should be high caloric and contain at least the minimal daily requirements of protein. Starvation diets are definitely to be avoided. Abdominal cramping may be quite disturbing. In general paregoric seems to accentuate this and increase the discomfort. If sedation and heat are ineffective, a small amount of codeine (½ to 1 grain) combined with atropine hypodermically is often effective.

The advent of the sulfonamides has proved to be a distinct contribution to the treatment and control of bacillary dysentery. The results of chemotherapy must be evaluated from the standpoint of (1) clinical cure of the disease, and (2) elimination of the Shigella from the stool so as to avoid the carrier state. In regard to the therapy of the acute phase of the disease many of the sulfonamides including sulfathiazole, sulfaguanidine and sulfasuxidine have been used and reported to be effective[15] with sulfasuxidine appearing to be particularly promising. Hardy[16] feels sulfadiazine is the most effective drug for the acute disease, and Poth and Ross[17] feel that sulfathalidine is the *drug of choice*. From these reports it is obvious that many of the sulfonamides are effective in treating bacillary dysentery. Variation in results reported by different authors as to the efficacy of the sulfonamides probably depends on the fact that different strains of Shigella found in various parts of the world vary in their susceptibility to different sulfonamides. In general most of them are susceptible to sulfadiazine, sulfa-

suxidine and sulfathalidine. For this reason we feel that as a rule the choice of a particular sulfonamide is related to the selection of one of the above three with the lowest toxicity. Hence, we prefer sulfathalidine given in doses of 4.0 grams daily. This drug is practically nontoxic, can be given even in the chronic cases over a long period of time and is quite effective. Our second choice is sulfasuxidine. It must be given in doses of six to twelve grams daily but occasionally may present some evidence of toxicity.

The other consideration in regard to chemotherapy, the avoidance of and elimination of carriers, has recently been investigated.[12] Streptomycin particularly has been studied in comparison with penicillin, sulfathalidine, and sulfasuxidine. It seemed to offer some promise with certain strains of Sh. paradysenteriae Flexner. However, several studies indicate that the sulfonamides are usually effective in eliminating the carrier state and we feel that this can best be accomplished with the use of the nontoxic sulfonamides and that sulfasuxidine and sulfathalidine are, at present, the drugs of choice.

Serum therapy can be dealt with briefly. It is usually necessary to employ the serum only in cases of severe Shiga infection. After testing the patient for sensitivity, 40 to 80 cc. of the serum diluted in 500 cc. saline are given intravenously. This may be administered twice daily until the severe toxemia is overcome. It should be remembered that the serum is antitoxic and not antibacterial and has no effect on the infection itself so that sulfonamides should be given simultaneously.

AMEBIC DYSENTERY

Amebiasis is a protozoan infection of man which initially is an enteric infection but which may give rise to foci of infection elsewhere in the body such as in the liver and lungs. The dysentery then is only part of what may be a more widespread protozoan infection. The infection is acquired in man by ingestion of the cysts of Endamoeba histolytica. In the ileum each cyst develops into eight trophozoites. The trophozoites then either invade the tissue of the intestinal tract or form cysts which are excreted in the stool. Two points in regard to this life cycle must be borne in mind: (1) The trophozoite is the form which is invasive, that is, it can invade the host's tissues and cause damage. (2) The encysted form on the other hand is not invasive, but is the infective form. In contrast to the trophozoite which is short lived when excreted in the stool, the cyst is resistant to changes in environment and is responsible for transmission of the disease. The spread of this disease in man is dependent on the human reservoir of the disease, that is, the human cyst-passer. From this reservoir the disease is transmitted largely through the contamination of food and water by several possible methods as, the use of human feces for fertilization, defective piping and plumbing, flies, and directly by the cyst passer himself through soiled hands. The latter method of spread is of particular importance in family outbreaks of the disease.

The clinical picture of amebiasis varies considerably and depends upon the localization of the amebae and the intensity of the infection. In addition, such factors as dosage, race of parasite, concurrent bacterial infection and duration of infection may greatly influence the symptomatology.[18] In general, for purposes of discussion of the clinical manifestations one may classify this infection as (1) intestinal amebiasis, (2) hepatic amebiasis, (3) and other forms of amebiasis.

Intestinal Amebiasis. Intestinal amebiasis may be asymptomatic (cyst-passers), acute or chronic. The asymptomatic infections or carriers usually have few symptoms, but dysentery apparently may develop whenever the general health is impaired by intercurrent infections, fatigue, exposure, or malnutrition. Carriers present many nondiagnostic manifestations such as constipation, mild diarrhea, underweight, colicky pains in the lower abdomen with or without tenderness, belching postprandially, slight nausea, mild headaches and the general picture of neurasthenia. Chronic microcytic anemia is not unusual. Some cyst carriers have periodic bouts of diarrhea with four to six liquid stools a day, associated with abdominal discomfort and cramping. Fever and tenesmus, as well as a leukocytosis are absent. This diarrhea may cease spontaneously and is then followed by a period of constipation and the other vague symptoms of the cyst carrier. This type of clinical picture which is a variation from the generally asymptomatic cyst carrier is often called amebic diarrhea. The physical examination in the asymptomatic cyst carrier, as well as in the case with amebic diarrhea is essentially negative aside from evidence of malnutrition and a moderate degree of pallor which may or may not be present. Diagnosis in this type of amebiasis is entirely dependent on the demonstration of cysts of E. histolytica in the stools.

Acute amebic dysentery has a more definite clinical picture. It is characterized by an incubation period of two to twelve weeks followed by the sudden onset of abdominal pain, vomiting, tenesmus, chilliness, and a temperature elevation, to about 102° F. There is a leukocytosis of 15,000 to 20,000. Iron deficiency

anemia may be present. Semiformed stools rapidly become liquid and contain bloody mucus. Finally, an almost continuous rectal discharge of blood-stained mucus and shreds of mucosa, exhaustion, lumbar aching, weakness of the legs and mental depression develop. There are several clinical variations in the acute form. Some may be milder while others are quite fulminating and may be complicated by bacillary dysentery or other pyogenic infections. The physical examination will demonstrate weight loss, evidence of toxicity, and tenderness over the course of the colon.

Chronic amebic dysentery usually results from repeated and inadequately treated attacks of acute dysentery or amebic diarrhea. This is usually the result of long continued mixed infection of the colon with bacteria and Endamoeba histolytica. It is associated with progressive scarring and deformity of the colon. The picture is characterized by recurrent attacks of fever and diarrhea with blood and pus in the stools. Often it is accompanied by malnutrition and cachexia. Clinically, it is difficult to distinguish from idiopathic ulcerative colitis, though x-ray examination of the colon is of help in that the deformity of chronic amebic dysentery usually starts around the cecum and ileocecal valve, but may later progress to involve other portions of the colon. This, of course, is in contrast to idiopathic chronic ulcerative colitis which generally arises in the most distal portions of the bowel. The type of intestinal amebiasis with ulceration of the cecum may give rise to the picture of amebic appendicitis which must be differentiated from the usual form of appendicitis.

Amebic hepatitis and abscess of the liver are serious complications of intestinal amebiasis. These may occur early in the course of the acute disease or after a prolonged period of chronic infection. They are the result of metastasis of the infection from the colon to the liver by way of the portal blood stream and possibly lymphatics. Depending on the duration of the amebic infection in the liver and the site of localization, the infection may give rise to the following clinical groups: [19] (1) acute abscess, (2) acute hepatitis, (3) subacute hepatitis and (4) chronic hepatitis. A definite history of intestinal amebiasis cannot always be obtained (as low as 13 per cent in some series), but often there is a history of intermittent diarrhea (63 per cent) suggestive of the disease.[20]

The clinical picture of amebic disease of the liver is usually characterized by the sudden onset of symptoms. The symptoms are often quite variable, but the most important are fever and liver pain. Occasionally there initially are diarrhea, chest pain and abdominal cramps, but the importance of the sudden onset of liver pain located in the right upper quadrant of the abdomen beneath the costal margin cannot be overemphasized as an important feature.[20] This pain is moderate in severity and characteristically is accentuated by a change in position. In addition to liver pain, fever, diarrhea, and abdominal cramps, cough must be considered an important symptom particularly with liver abscess. The physical examination usually reveals an acutely or moderately ill patient with occasionally evidence of some weight loss. There may be a sallow complexion. Clinical jaundice is rare.[20] Subcostal tenderness, palpable enlargement of the liver and particularly compression tenderness of the liver are diagnostically important. X-ray examination of the chest may show evidence of slight atelectasis on the right and immobility of the diaphragm. Occasionally, local bulging of diaphragm by x-ray is diagnostic of abscess. Other laboratory findings are a leukocytosis and presence of cysts of E. histolytica in the stools (in 80 per cent of the cases [20]).

Other forms of amebiasis are comparatively rare. These include [13] amebic abscess of the brain, amebic infection of the skin and subcutaneous tissue, amebic abscess of the spleen and epididymis, urinary amebiasis and pulmonary amebiasis. The latter may be the result of either direct extension from liver amebiasis or direct metastatic infection from the colonic wall. Pulmonary amebiasis and cutaneous amebiasis are occasionally seen but most of the other forms are comparatively rare and unimportant from the standpoint of total incidence.

Diagnostic Methods

Diagnostic methods employed in all forms of amebiasis are (1) stool examination, (2) sigmoidoscopy, (3) roentgen examination, and (4) blood studies. The stool examination is the most important. Gross inspection is of little help. The stool must be fresh and to demonstrate the E. histolytica it may be necessary to administer a saline purge. This is usually not necessary during acute diarrhea. During acute amebic dysentery the cytology of the stool is important and reveals the absence of pus cells. If red cells are present they appear in clumps. The lack of cellular elements in the stool is in direct contrast to the picture seen in acute bacillary dysentery. To search for amebae a fleck of mucus or blood from the fresh stool is placed on a slide, mixed with warm saline and an immediate search made for active trophozoites. If no trophozoites are present the saline suspension is stained with iodine and a search made for cysts. Con-

centration and flotation methods of stool examination should be employed if direct examination is negative. Often blood or mucus wiped from an ulcer visualized at proctoscopy reveals the trophozoites when not found by direct stool examination.

Sigmoidoscopy is valuable to rule out other conditions and may make it possible to visualize the characteristic ulcerations surrounded by intervening normal mucosa. However, the great value of sigmoidoscopy is to avoid delays and overcome difficulties in obtaining warm stools for examination. With sigmoidoscopy material can be obtained directly from the lesion in the mucosa and the diagnosis may be made more rapidly. Roentgen examination is of value, first of all in the chronic cases where by barium enema it is possible to localize the disease in the colon, particularly near the cecum and thus rule out other conditions such as chronic idiopathic ulcerative colitis. X-ray of the chest and diaphragm are of help in the diagnosis of amebic disease of the liver. Blood studies are only of value in indicating presence of leukocytosis and/or anemia. Eosinophilia is not a characteristic feature.[20]

Treatment

As in the treatment of bacillary dysentery, the treatment of amebiasis is both symptomatic and supportive, and chemotherapeutic. The symptomatic and supportive therapy is essentially alike in both conditions and should include rest in bed and a low-roughage diet. For severe cramps, the use of 0.032 Gm. of phenobarbital and 0.032 Gm. of codeine every four hours as needed is valuable. If dehydration is a problem, it is best corrected by use of isotonic saline intravenously. The chemotherapeutic phase of treatment has always been based on the use of emetine which dramatically relieves the symptoms of amebic dysentery, but experience has indicated that it may fail to cure.[21] Moreover, serious toxic reactions to the drug have been described. As a result, current opinion limits its use to the control of symptoms and favors the newer iodine and arsenic compounds for eradication of the parasite.[21] In addition, because bacillary dysentery is a complication is about ten per cent of the cases of acute amebic dysentery [22] it has been urged [23] that sulfonamides and penicillin be used as preparatory medication to use of amebicidal drugs. Bearing these points in mind, modern therapy for amebic dysentery can be summarized as follows: [22]

1. Emetine hydrochloride, total of five to six grains (0.3 or 0.36 Gm.) in divided doses of 1 grain (0.065 Gm.) daily. This is usually adequate for the asymptomatic cyst-passer or the case with mild amebic diarrhea. For more massive invasions, such as acute dysentery and hepatitis, emetine is given up to a full total dose of 10 grains (0.6 Gm.). British investigators [24] also feel that emetine orally as emetine-bismuth-iodide is of value, 2.0 grains nightly for 12 days. However, most American authors have not had much experience with this preparation.

2. Simultaneously, chiniofon 0.5 to 0.75 Gm. three times daily for ten days and sulfadiazine 1.0 Gm. every four hours for a total of 20.0 Gm. Diodoquin (0.6 Gm. three times daily) may be substituted for the chiniofon.

3. Carbarsone, 0.25 Gm. three times daily for ten days. This usually is given after the chiniofon, but some authors prefer to give the carbarsone first and then follow this with the chiniofon.

4. Surgical drainage may rarely be necessary in hepatic amebiasis, particularly abscess. If treatment is started early and adequate emetine is administered, one may decrease the number of cases requiring surgical drainage.[19] If surgical drainage is necessary, it must be accompanied by the use of amebicidal drugs to eradicate the protozoa. In addition, it should be remembered that laparotomy should be carefully avoided in the presence of amebic infestation, in view of the high operative mortality.

All of the amebicidal drugs may show evidence of toxicity, particularly emetine. The main toxic effects of this drug are diarrhea, cardiac irregularities and muscular tremors and weakness and finally neuritis.[20] Early symptoms should be looked for and when they occur the drug should be discontinued. The iodine drugs may cause nausea, vomiting and diarrhea, but no other serious reactions. Carbarsone should not be given to individuals sensitive to arsenic.

SUMMARY

1. The dysenteric disorders are classified as (1) food poisoning, (2) bacillary dysentery, and (3) amebiasis.

2. The importance of the correct etiologic diagnosis is stressed in view of the recent advent and use of various specific chemotherapeutic drugs in their treatment. Accurate diagnosis is based on laboratory information, but the clue to etiology is often supplied by a careful history and physical examination.

3. The clinical pattern and important diagnostic features of each type are reviewed with emphasis on the use of laboratory and x-ray methods of diagnoses.

4. Food poisoning is widespread, but generally the least serious of the dysenteric disorders. Bacillary dysentery and amebiasis are more serious, so that delay

in diagnosis or inadequate therapy may lead to complications and chronic, prolonged illness.

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Small Chance of Conquering Cancer?

Conquest of cancer is one of the most hopeless problems of science if the theory proves true that tumor growth is caused by changes in the form of the genes, the fundamental units controlling inheritance.

Dr. George W. Beadle of the California Institute of Technology, in delivering a Silliman lecture at New Haven, Conn., in connection with the centenary of Yale's Sheffield Scientific School, explained that while the frequency of mutations of the genes can be increased in many ways, there is little immediate hope of decreasing them.

Progress in cancer research is discouragingly slow, he emphasized, although great sums of money are being spent and an impressive array of talent is directed upon this problem. The idea that change in the fundamental living bits that carry heredity is the fundamental cause of cancer is very discouraging and Dr. Beadle feels that makes scientists reluctant to look with favor on the idea.

Radiation from the atomic bomb, x-rays, cosmic rays, and even the ultraviolet light in strong sunshine are all known to be able to cause change in the inheritance of living things, human beings included. Radiations do this by changing the genes. Some of the changes may not show up until scores of generations have lived and died. This is the basis of the real fear that some scientists have of the genetic disaster for mankind and other living things contained in the atomic bomb.

——From *Science News Letter*, October 25, 1947.

The authors review the anatomic changes in syphilitic aortitis. The clinical manifestations in the complications of aortitis are presented, especial attention being given to aneurysm. The modern treatment of aortitis is considered as well as newer surgical approaches to the management of aneurysm.

Syphilitic Cardiovascular Disease*

An Analysis of 59 Cases of Aortic Aneurysm and a Review of Modern Concepts of Treatment

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Syphilis continues to be the etiologic factor in 10 to 15 per cent of all cardiovascular involvement. One of the vascular manifestations of syphilis is aneurysm. Internal ones were first recognized in the 16th century by Fernelius,[1] and in this same period Paré [2] suggested the relation of aneurysms to syphilis. Definite proof was not established until the presence of Treponema pallidum in the wall of the aorta in aortitis was reported by Reuter in 1906.[3] In spite of the fact that several good surveys have been made of the subject, the diagnosis of aortic aneurysms continues to be difficult. It was for this reason that a study of 59 cases was undertaken along with a brief review of the pertinent literature. Some of the newer concepts of treatment are also presented.

The primary and earliest vascular lesion in syphilis consists of a lymphocytic perivascular infiltration of the vasa vasorum followed by an obliterature endarteritis of these vessels. Medial changes are secondary to the adventitial change, as a result of decreased nutrition with ultimate elongation or dilatation in many cases. The rich supply of the vasa vasorum at the root of the aorta accounts for the high frequency of syphilitic involvement in this area. Syphilis then spreads from the aorta to the aortic valves by way of the small vessels at the commissures. Degenerative and chronic inflammatory changes occur causing fusion of the lateral margins of the leaflets with the adjacent aortic intima, and thereby, widening of the commissures. The coronary ostia became involved in approximately one-third of the cases. Occasionally aneurysms of the subclavian, innominate, mesenteric, iliac, or femoral arteries are present also. It is rare, however, to have invasion of the myocardium by the Treponema. The anatomic alterations recognized clinically, therefore, are aortic aneurysm, coronary ostial involvement, and aortic insufficiency. Aortitis per se, without one of these three lesions, cannot be diagnosed clinically.

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INCIDENCE

Aneurysms of the aorta may occur at almost any age. Some of the youngest have occurred in so-called congenital syphilis at the ages of seven and 17 years.[4] However, aneurysms occurring before 30 years of age are rare. The average onset is 15 to 20 years after a chancre. Maynard et al.[5] found that the onset occurred within three years of the primary infection in 14 per cent of 346 cases and within ten years in 25 per cent and that the average latent period was 20 years. It is to be noted in Table 1 that the highest incidence in our patients occurred between 30 and 60 years with about an equal distribution in each of those three decades.

TABLE 1

Incidence of Aneurysm by Age Groups

AGE	CASES	PERCENTAGE
30–40 years	15	25.4
40–50 years	16	27.1
50–60 years	15	25.4
60–70 years	9	15.3
70–80 years	4	6.8

The predominance of aneurysms of the aorta in males in our study, 46 of 59 cases of 78 per cent, confirms other studies.[6] They were more frequent in the Negro race, 43 of our 59 cases or 72.7 per cent, Caucasians accounted for 12 instances, 20.4 per cent, and Mexicans for the remaining four, 6.9 per cent.

Arkin [6] found also that aneurysms occurred four times as frequently in Negroes as in Caucasions. Perhaps it may be due, in part at least, to a higher incidence of hypertension in the Negroes, a more frequent neglect of treatment, and their engaging in a greater amount of hard labor.

A history of a primary chancre was obtained in 15 of our 59 cases, 25.4 per cent. According to the records, treatment was not obtained in 40 cases, 67.8 per cent. It was grossly inadequate, 10 injections or less, in ten cases, 16.9 per cent, and only partially adequate, ten or more injections, in nine cases, 15.3 per cent. In Moore's [7] series, 90 per cent had had no previous treatment. He stated that if a patient had received as many as 24 injections of an arsenical, cardiovascular syphilis would not develop.

SYMPTOMS

Osler tried to impress his students with the etiologic triad of Venus, Bacchus, and Vulcan and to this Butler [8] thinks that perhaps Mars should also be added. The subjective manifestation of our 59 cases appear in Table 2.

TABLE 2

Subjective Manifestations of Aneurysm

SYMPTOMS	CASES	PERCENTAGE
Shortness of breath	26	44.0
Chest pain	17	28.8
Brassy cough	13	22.0
Hemoptysis	11	18.6
Dysphagia	7	11.8
Hoarseness	7	11.8
Asymptomatic	6	10.1

Pain is a fairly frequent symptom of aneurysm. It may result from erosion of a bony structure, pressure on a nerve trunk, or involvement of the coronary ostia. Exertional or paroxysmal dyspnea may result from compression of the trachea or a bronchus. Hoarseness and brassy cough may be due to involvement of the left recurrent laryngeal nerve (aneurysm of the transverse portion of the aortic arch) or of the right laryngeal nerve (aneurysm of the innominate artery). Dysphagia results from pressure on the esophagus in aneurysmal involvement of the descending aorta, and it was noted in seven of eleven such patients. Hematemesis as a result of esophageal erosion may occur. Other subjective manifestations, not specifically resulting from the aneurysm, were due to cardiac failure by and large. The descending aorta is frequently known as the "aneurysm of symptoms" because pressure effects on the esophagus, trachea, and bronchi occur fairly early. The first manifestations noted by the patient in aortic insufficiency [9] are usually those of early heart failure with dyspnea, palpitation and edema predominating.

PHYSICAL FINDINGS

The aneurysms of the ascending aorta are frequently referred to as the "aneurysms of findings." According to Korns [10] in about 90 per cent of the cases, the principal involvement is of the valve and ascending portion of the aorta. This circumstance is fortunate, for syphilitic aortitis is recognizable in its earliest stages only when the root of the aorta is involved.

The composite physical findings in 59 cases examined by many different clinicians may be noted in Table 3. This may be contrasted with Table 4 which shows the composite findings in nine cases examined by men especially interested in the disease. It is evident that the increased thoroughness of examination enables a more correct diagnosis to be made.

TABLE 3

Composite Physical Findings in 59 Cases

FINDING	CASES	PERCENTAGE
Systolic murmur	37	62.7
Accentuated 2d aortic sound	23	38.9
Widened mediastinum	21	35.5
Aortic insufficiency	17	28.8
Cardiac failure	17	28.8
Brassy cough	13	22.0
Tracheal tug	10	16.9
Palpable pulsation	10	16.9
Hoarseness	7	11.8
Visible pulsation	5	8.4
Retromanubrial pulsation	4	6.7
Unequal pulses	4	6.7
Upper sternal dullness	4	6.7
Paralysis of left vocal cord	4	6.7
Nodding of head	3	5.0
Atelectasis left lung	3	5.0
Paralysis right vocal cord	1	1.6
Pulsation—innominate artery in neck	1	1.6

The earliest physical findings of aortitis are auscultatory. Potain [11] first called attention to the tambour or bell-like second aortic sound which is frequently the first physical sign of increased accessibility. When the disease process is limited to the ascending portion beyond the valve, the tambour or bell-like second aortic sound appears earliest, and in addition the following physical findings may occur: A systolic murmur [9] may become manifest and is probably due to dilatation of the artery. Then a palpable systolic impulse may be felt as a result of propulsion of the chest wall by the aorta, and in addition a diastolic impact is perceived due to the vibration set up in the chest wall by the sudden closure of the aortic valve. These

TABLE 4

Composite Physical Findings in Nine Cases

FINDING	CASES	PERCENTAGE
Systolic murmur	8	88.8
Accentuated second aortic sound	6	66.6
Aortic insufficiency	4	44.4
Upper sternal dullness	4	44.4
Widened mediastinum	3	33.3
Retromanubrial pulsation	3	33.3
Brassy cough	3	33.3
Hoarseness	3	33.3
Paralysis of left vocal cord	2	22.2
Cardiac failure	2	22.2
Tracheal tug	2	22.2
Palpable pulsation	2	22.2
Unequal pulses	2	22.2
Paralysis of right vocal cord	1	11.1
Atelectasis left lung	1	11.1

findings can be obtained earlier and better by palpation with the head, probably because of the labyrinthine receptors located there. Normally these pulsations are imperceptible over the aorta, but with its enlargement they become palpable. As a rule, no large pulsation is accessible to palpation in the retromanubrial space. The innominate artery or the aorta itself, however, may be rendered readily accessible by arteriosclerotic elongation or aneurysmal dilatation. On percussion the increased dullness over the upper sternum similar to that obtained over the lower sternum may next appear. Parasternal dullness to the right in the second interspace may develop. A visible systolic impulse is the last physical sign to appear in aneurysms of the ascending aorta or arch and indicates extreme accessibility. Rarely, cyanosis results from pressure on the superior vena cava or compression of the pulmonary artery.

When the disease involves the valve rings, cusps or ascending portion of the aorta, all of the physical signs detailed above may be present, in addition to those of aortic insufficiency.[10] The accentuation and tympanic quality of the aortic second sound and the diastolic impact are inversely proportional to the degree of valvular insufficiency. The first evidence of a developing aortic insufficiency is the presence of a diastolic murmur over the anatomic site of the aortic valve or along the left border of the sternum. It is frequently best heard with a diaphragm type of stethoscope [12] at the end of the deep expiration with the patient leaning forward in the sitting position. In contrast to mitral stenosis, it begins immediately with the second sound, is steadier and is of higher pitch.[9] It may be intermittent at first, transmitted downward toward the apex, and may be occasionally accompanied by a palpable thrill. The Corrigan type of pulse with a large volume and a celer contour is classical in this condition. Duroziez's phenomena, spontaneous arterial sounds and capillary pulse may be present. A large mean pulse pressure commonly occurs as a result of some elevation of the systolic arterial pressure and a very pronounced depression of the diastolic pressure. Selective left ventricular hypertrophy as a result of increased heart volume, is manifested by extension of the left heart border beyond its normal limits, a vigorous, localized, apical systolic impulse, and a diminished outward movement of the medial half of the left costal margin.

When syphilitic involvement is limited to the arch, the earliest sign again is an accentuated aortic second sound and a systolic aortic murmur. Depending on its degree of development, a systolic impulse and diastolic impact may be palpable and if further extension of the process occurs a retromanubrial pulsation may be felt and seen. Percussion may reveal upper sternal and parasternal dullness both to the right and left in the second intercostal space. At times a tracheal tug which is manifested by a systolic descent of the trachea due to enlargement of the aorta crossing the left main bronchus is elicited. The recurrent laryngeal branch of the left vagus nerve is frequently encroached upon by aneurysm of the arch of the aorta resulting in paresis of the left vocal cord leading to cough, hoarseness, and aphonia. Horner's syndrome may occur as a result of involvement of the cervical sympathetic chain or its ganglia.

Unilateral diminution of pulse volume in the carotid and brachial arteries, accompanied by lower arterial pressures, may, if permanent and of sufficient magnitude, indicate that disease of the aorta has encroached upon the orifices of the innominate, left common carotid, or left subclavian arteries. Normal subjects may show some disparity in volume and pressures of the two sides, but they will usually have the smaller pulse and lower arterial pressure on the left side.

The descending portion of the aorta is so inaccessible that unless the dilatation is very large it is likely to escape detection. At times it may cause marked compression of the esophagus with resulting dysphagia. Atelectasis may occur from bronchial obstruction. Sosman [13] thinks that aneurysms are more likely to cause partial compression of the bronchus with the production of obstructive emphysema due to a ball-valve type of obstruction. He thinks also they are usually located in the left upper lobe.

One of our patients complained of hoarseness, cough, and shortness of breath; a paralysis of the right vocal cord was found to be due to aneurysm of

the innominate artery. There was also an associated right Horner's syndrome from pressure on the right cervical sympathetic chain. Other signs associated with aneurysms of the innominate artery include dyspnea and dysphagia as phenomena of pressure on the trachea and esophagus. Venous congestion and cyanosis of the head and upper extremities may occur as a result of pressure on the superior vena cava.

Occasionally, compression [14, 15] of the pulmonary artery by an aneurysm occurs. It may be recognized when the physical signs of aortic involvement are present with those of cor pulmonale superimposed. When rupture [16] of the aneurysm into the pulmonary valve area develops a continuous murmur ensues. About 3.7 per cent [17] of aortic aneurysms rupture into the pulmonary artery.

Stigmata of syphilis other than that of the cardiovascular system, such as Argyll-Robertson pupils, enlarged epitrochlear glands, scars, or evidence of central nervous system involvement may help make the diagnosis. These are listed in Table 5.

TABLE 5

Associated Syphilis of Central Nervous System

MANIFESTATION	CASES	PERCENTAGE
Tabes dorsalis	2	3.3
Meningovascular involvement	3	5.0
Paresis	1	1.6

TABLE 6

Aneurysms Associated With Other Disease

DISEASE	CASES	PERCENTAGE
Pneumonia (lobar)	2	3.3
Tuberculosis	3	5.0
Pleural effusion	1	1.6
Chronic glomerulonephritis	1	1.6

It will be noted from Table 6 in our series that only a small number of the aneurysms were associated with other disease.

Roentgenograms [18] are valuable for the correct localization of the aneurysm, to judge its size and to ascertain possible pressure points resulting from it. The location of our aneurysms can be seen in Table 7. Roentgenograms [5] and fluoroscopic examinations

TABLE 7

Location of Aneurysm (Roentgenogram)

LOCATION	CASES	PERCENTAGE
Ascending aorta	33	55.9
Arch of aorta	30	50.1
Descending aorta	11	18.6
Multiple aneurysms of the aorta	15	25.4

provide the most reliable method to detect whether or not abnormalities of the aorta are present in syphilis. The oblique positions are the best to prove definitely the presence of an aneurysm. According to Steel,[12] one may suspect the presence of syphilitic aortitis if there is a marked degree of generalized dilatation of the aorta, especially when the heart shadow is small or when it occurs in a person under 40 years of age. Secondly when a dense, high aorta is present in a young individual without hypertension. He further believes that aneurysms can accurately be diagnosed when there is localized dilatation with localized increased pulsation, and especially so if it is accompanied by the characteristic heart shadow of aortic insufficiency. Schwedel [19] states that aneurysms may be suspected if a dense mediastinal mass, usually with smooth borders, is observed to be a part of the aorta in all degrees of rotation.

The majority of the syphilitic aneurysms are saccular and occur most often in the convex portions of the aortic arch. Fusiform aneurysms are most frequently seen in the descending thoracic aorta and may be associated with saccular aneurysms in other parts of the aorta. A saccura aneurysm may attain enormous size and at times is associated with small "daughter aneurysms."

Expansile pulsations are more often seen in the earlier stages of development of saccular aneurysms. But, quoting Schwedel,[19] "the presence of thrombi, calcification or peri-aortic adhesion may modify the degree and type of pulsation so that the absence of pulsations is not a satisfactory criterion for the absence of aneurysm. In fusiform aneurysms, where thrombi are usually absent, expansile pulsations are usually seen."

Aneurysms involving the ascending aorta usually occur on the convex portion of the vessel and are frequently round bulging tumors.[12, 18] They may extend into the right lung field anteriorly when viewed in the right anterior oblique position and occasionally may project into the anterior mediastinum on the left. They may cause pressure and erosion of the sternum and ribs, or pressure on the pericardial sac with possible rupture into it, or compress the bronchus causing atelectasis and bronchiectasis, or compress the pulmonary artery or superior vena cava.

Aneurysms located in the transverse portion of the aorta may extend anteriorly or posteriorly and to the left. Erosion of the left anterior aspects of the fourth, fifth, and sixth vertebra may occur with them. If the aneurysm of the arch is small, it may be hemispherical and point backwards; however, if it is a large aneurysm, it may hang posterior to the pericardial sac.[12, 18]

Aneurysms in the descending thoracic aorta may project to the left or anteriorly and may be visualized

as a bulge or an area of increased density on roentgenograms taken in posteroanterior and the oblique positions. Large aneurysms may extend to the right of the heart shadow. When they are located in the upper descending aorta they are frequently oblong and roughly elliptical in shape; when located in the middle descending portion they are frequently boot type, and these are said to have the best prognosis.[12, 18]

Aneurysms of the innominate artery may be located in the upper or lower portion of the vessel. They may press on the sternum, clavicle or spine. If an aneurysm occurs at the junction of the aorta and the innominate artery, the trachea, and heart may be displaced downward. Fluoroscopy [6] may reveal a throbbing aneurysmal dilatation in the right supraclavicular fossa which may or may not extend into the aorta. Both right and left oblique views should be employed in examining for its presence.[6]

In differentiating between aneurysm and lymphoma, there is usually no displacement of the esophagus or treachea with a lymphoma. Thoracic aneurysms as a rule do not erode the vertebra, however, when this occurs the intervertebral disks are not destroyed. Lymphomas decrease in size rapidly after roentgen ray therapy. Finally diodrast may enable better visualization and localization of the aneurysm.

Jackman and Lubert [20] found linear calcification present in 22.7 per cent of their cases of syphilitic aortic aneurysm in contrast to 3.2 per cent in a control series of arteriosclerosis of the aorta. Calcification is not an early sign, however, and occurs most often in older, relatively quiescent cases of syphilis. An enlarged pulmonary artery and conus [15] may occur as a result of compression of the pulmonary artery by an aneurysm. Erosion of the spine was noted in three of five cases of dysphagia reported by Arkin [6] due to aneurysms of the descending aorta. Administration of barium paste enables one to measure the size of the descending portion of the arch from the concavity in the esophageal wall to the left border (Kreuzfuch's method). Rarely do aneurysms of the subclavian artery cause erosion of the right clavicle. Occlusion of the left main bronchus by an aneurysm may lead to atelectasis of the left lung; an even more unusual complication of an aneurysm involving the arch or descending aorta is an associated left pleural effusion.

The roentgen findings in syphilitic aortic insufficiency [21] are: (1) An increase in the supracardiac shadow, which is usually found just above the heart shadow, to the right of the sternum in the region of the aortic valve; (2) abnormal pulsations in the region of the ascending aorta; (3) a cone shaped supracardiac shadow; (4) flattened aortic knob; (5) pyramid-like shadow extending upward from the aorta in the region of the innominate and subclavian arteries; and (6) changes in the appearance of the heart shadow, either a moderate generalized enlargement accompanied by a poorly defined left ventricular and flabby beat or a marked enlargement of the left side of the heart with a blunt apex and horizontal position.

Other Tests. The other laboratory examinations which may be included in making the diagnosis of aneurysms consist of serologic tests for syphilis and possible abnormalities in the electrocardiographic tracings. In our series, 54 of the 59 cases, 91.5 per cent had a positive Wassermann reaction. A negative serologic test for syphilis does not exclude the possibility of syphilitic aneurysms. In Levine's [13] series, 20 to 25 per cent of autopsied patients with syphilis aneurysms had negative blood Wassermann's, but with the Hinton test only 10 per cent gave negative results. Arkin [6] found the Wassermann to be negative in 25 per cent of his series. Electrocardiograms are of little or no value in the early diagnosis of syphilitic cardiovascular involvement. Steel [12] found no changes in 27 cases. However, Blackford and Smith [22] observed that the prognosis was much worse in those individuals in whom low voltage, QRS slurring, or low voltage of the T waves occurred. Electrocardiograms were obtained in only seven of our series of 59 cases, and the only questionably significant finding among these was the presence of left-axis deviation in four.

TREATMENT

Syphilitic cardiovascular involvement is one of the forms of preventable heart disease and 90 per cent and more could be prevented if syphilis were diagnosed in the primary stage and sufficient treatment were given.[6] Adequate treatment with courses of one of the heavy metals and an arsenical, or with penicillin, could prevent the development of aortic involvement in a vast majority of cases. In Kemp and Cochems' [23] 249 cases, only 0.4 per cent of adequately treated patients followed over a ten-year period, developed cardiovascular involvement. With inadequate treatment 7.4 per cent developed it, and with no treatment 18 per cent developed it.

It is recognized [24] that once the lesion has become established treatment does not change the cardiac incompetency nor the anatomic condition. It is hoped, on the other hand, that the process will be arrested without further progression. Howe [25] and Hood and Mohr [26] have found no difference in the pathologic appearance of the treated and untreated cases.

The initial administration of potassium iodide and either bismuth or mercury for 10 to 12 weeks,[27] followed by arsenicals has been an accepted method of medical treatment of cardiovascular syphilis. Mapharsen or neoarsphenamine have been used, but very small doses of the arsenicals have been employed with gradual increase in amounts up to approximately one half the adult dose. Then alternating courses of the heavy metals and the arsenicals are carried on for two years with appropriately spaced rest periods.

Obviously the above outlined therapy has to be modified depending upon the location of the lesion. If there is supravalvular involvement[28] and no encroachment on the coronary ostia, as determined by the absence of anginoid attacks or electrocardiographic changes, fairly intensive treatment, as outlined above, may be initiated. By careful treatment in this type of early case, the lesion may be arrested and encroachment on the coronary ostia avoided. When aortic regurgitation is present intensive treatment is of little value and is thought by some to be definitely dangerous. If cardiac failure is present no specific antiluetic treatment should be attempted. When the coronary ostia are involved, the greatest care should be exercised in the adequate preparation of the patient with bismuth and potassium iodide. Too intensive treatment may be followed by a Herxheimer reaction with edema of the coronary orifices and sudden death. Too intensive treatment with arsenicals may cause too rapid healing and lead to extensive scarring. In patients with thoracic aneurysms located above the root of the aorta, especially if there is considerable periaortitis and mediastinitis, they may be greatly benefited from treatment, but again extreme care in treatment is advisable. There is some danger in giving intensive treatment if there is any evidence of marked thinning out of the wall.

More recently we have been employing penicillin in the treatment of aortic aneurysms in an attempt to partically evaluate its place in the realm of therapy. In our opinion, a three months' preliminary period of treatment with iodides and bismuth may be indicated, but more recently initial penicillin therapy has been employed in some cases. Because of reports of Herxheimer reactions in penicillin-treated cases of cardiovascular syphilis,[29] we have started with a small initial dose of 10,000 units of penicillin intramuscularly, followed by 15,000 units and then 50,000 units given at two-hour intervals. A total of approximately six million units are administered. In addition, potassium iodide is given orally each day and bismuth injected intramuscularly every other day during the course of treatment. We have used this method of therapy in patients who have had demonstrable aneurysms and who show no evidence of cardiac failure. When cardiac failure is present, we think that antiluetic therapy is useless. If angina is present extremely careful observation during the period of penicillin administration is indicated, but in two cases with angina a marked lessening in the pain was observed. We have not lost sight, however, of the efficacy of potassium iodide, bismuth and the arsenicals. It is too early to evaluate our results from this type of therapy although some rather good subjective response as far as relief of pain has been seen, but no objective change has been noted in any of the cases.

Stratton[30] thought that antisyphilitic treatment in the case of syphilitic aneurysm was responsible for prolonging life from 12 to 16 months in 200 observed cases. In 161 of Padget, Paul, and Moore's[31] patients the authors thought that adequate treatment prolonged life about 20 months. The benefits derived from treatment are largely symptomatic,[32] chiefly in the form of relief from pain. Hines and Carr[32] found there was an increased period of relief of pain for an average of 14 months in 57 per cent of his patients. Twelve per cent had an aggravation of their symptoms. Improvement in the blood Wassermann test does not always parallel symptomatic improvement. There is a much higher percentage of improvement if aortitis exists alone without aneurysm or regurgitation. Grant[33] thought that properly directed antiluetic treatment may prolong life in two-thirds of the patients with saccular aortic aneurysms or insufficiency. The remaining one-third come under observation with an initially bad prognosis and do not survive sufficiently long for proper treatment.

Surgery. The first surgical method employed in treating aneurysms was the injection of small metallic particles into the aneurysmal sac to promote clotting.[34] The particles frequently escaped into the systemic circulation and caused immediate death. It was for this reason that this method was abandoned. The next procedure used was the threading of 30 to 200 feet of fine silver or copper wire into the aneurysmal sac and passage of a Galvanic current through the wire to encourage thrombus formation.[35] Too frequently leakage occurred with this method. External compression of the wall of the vessel was attempted next by means of a rubber tube, a metal clamp,[36] or a fascial strip. Pressure atrophy and infection through the sinus tract caused relinquishment of this method.

The latest surgical approach to aneurysms is external irritation of the vessel wall to cause fibrosis and constriction. The first attempts at this method were painting the vessel with irritating dyes and other scle-

rosing substances. These proved to be too traumatic and ineffectual. Then in 1939, Page [37, 38] wrapped a dog's kidney with cellophane thinking it would be nonirritating. On the other hand, a dense fibroblastic and collagenous deposit three to five millimeters in thickness was formed about the kidney in a period of two weeks. In 1940, Pearce [39] first experimented with cellophane wrapped around blood vessels in dogs. He found that the cellophane slowly thickened the wall and occluded the lumen. In 1943, Harrison and Chandy [40] first put this knowledge into practice in a human patient in treating an aneurysm of a subclavian artery. In ten months the aneurysm began to reduce in size and five months later the dilatation was completely reduced. By the end of 19 months the vessel had become occluded. In 1944, Harper and Robinson [41] successfully occluded a patent ductus arteriosus by wrapping it with cellophane. In June 1946, Pope and de Olvera [34] reported the successful use of this method of cellophane wrapping in the treatment of syphilitic aortic aneurysm. They employed polythene cellophane in wrapping an aneurysm involving one-third of the descending aorta. Partial disappearance of the pain was noted in 13 days after the operation and complete relief in three months. They covered the outside of the polythene cellophane with 300 P.V.T. No. 71 to prevent the polythene cellophane from reacting with the other tissues and causing dense adhesions.

Abbott [42] has successfully wrapped ten cases of aneurysm with polythene cellophane. In those patients who were having pain there was immediate relief, and it had not returned. At times a first stage decompression is done, i.e., parts of the clavicle, ribs, or sternum may be removed to take the pressure of the aneurysm off of the pulmonary bronchus. He thinks all parts of the intrathoracic aorta as well as the innominate, subclavian, and pulmonary arteries can be wrapped successfully.

We have had one patient with an aneurysm involving the arch of the aorta which was wrapped with polythene cellophane, and the patient obtained immediate relief from the pain. Further studies of surgical procedures are in progress and will be reported in detail at a later date.

Lewis [43] observed that the average duration of life in uncomplicated aortitis without treatment and no superimposed heavy work was six years, but with the presence of an aneurysm he believed it to be about four years. White [44] thinks that the average duration of life is two to three years with an aneurysm, and he believes that strenuous activity definitely shortens this span. Friedlaender [18] states that the best prognosis is in those patients with aneurysms that are well localized. In 22 per cent of his cases the lesions came to a standstill clinically and roentgenographically. Boot-shaped aneurysms of the middle part of the descending aorta give a better prognosis than the ascending aorta or arch. Ten to 20 per cent of all patients with syphilitic aneurysms die as a result of rupture or pressure on adjacent tissues. The majority, however, die as a result of involvement of the coronary ostia or heart failure.

SUMMARY

The subjective and objective manifestations of 59 cases of syphilitic aneurysm of the aorta have been analyzed. The symptoms, physical findings, diagnosis, roentgenograms, laboratory studies, and methods of treatment including the employment of penicillin and certain more recent surgical technics are discussed.

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Annual Convention of American Academy of Allergy

The American Academy of Allergy will hold its annual convention at Hotel Jefferson, St. Louis, Missouri, December 15–17 inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy by registering without payment of fee. The program, the scientific, and technical exhibits have been arranged to cover a wide variety of conditions where allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as the results of investigation and research. Round table conferences will be held on Monday afternoon, December 15, 1947. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Charles H. Eyermann, M.D., 634 North Grand Boulevard, St. Louis, Missouri.

The author emphasizes the disturbed physiology in hypoparathyroidism. The possibility of a predisposition to cataract formation is a most practical issue.

Comments on Hypoparathyroidism and Cataract Formation*

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The most frequent cause of hypoparathyroidism is the accidental removal of or injury to these glands during thyroidectomy. Their variation in number and location predisposes to such accidents. However, this is a rare complication of thyroidectomy, occurring in less than one per cent of some 1,100 thyroidectomies performed in the Vanderbilt University Hospital. Operations for hyperparathyroidism are followed at times by hypoparathyroidism. Spontaneous parathyroid insufficiency occurs even less frequently.

Regardless of the causative mechanism, hypoparathyroidism results in a lowering of the blood calcium and, if this is of sufficient extent, the development of tetany. Transient slight lowering of the blood calcium is seen not infrequently during the first day or two following thyroidectomy. This is of no importance and is apparently due to temporary interference with the blood supply of one or more of the parathyroid glands. The normal serum calcium level is from 9 to 11 mg. per 100 cc. Tetany usually occurs at levels of less than 7 mg. per cent and results from an imbalance of blood electrolytes, the low serum calcium resulting in a relative excess of sodium, this causing hyperexcitability of various muscle groups. The upper extremities may show the carpal spasm in which the hand assumes the "obstetric" position. When the lower extremities are involved the legs are extended with plantar flexion of the feet and toes. These two characteristics of the tetanic state make up the so-called carpopedal spasm. Chvostek's sign may be elicited by tapping over the facial nerve in front of the ear resulting in contraction of the muscles about the mouth on this side.

Spasm of laryngeal muscles may occur, particularly at the onset of severe tetany. This has occasionally led to tracheotomy, but this should not be required if the tetany is recognized and properly treated. The vocal cords assume the position of abductor paralysis leading to approximation of the cords and stridor. Fever, at times of considerable degree, may be found during the acute phase and pain during severe muscle contractions may be prominent. The complaint of stiffness and aching is common when the serum calcium level is slightly above the level at which frank tetany occurs.

Once tetany of this type occurs treatment is urgently needed. Striking and rapid relief is afforded by the intravenous injection of a suitable calcium preparation. Ten cubic centimeters of 10 per cent calcium gluconate solution may be expected to abolish tetany within a few minutes. This dose should be repeated if no relief has occurred after 15 minutes or so. Three or four such intravenous injections per day will ordinarily be sufficient. However, it is obvious that the maintenance of satisfactory blood calcium levels by this means is feasible for short periods of time only. Since persistent hypocalcemia is to be expected other measures must be employed. Parathyroid hormone (parathormone) is of limited value. It is effective in elevating the serum calcium level, but this effect is delayed for four hours or more and its continued use leads to refractoriness.

Calcium salts given by mouth are of value, but alone they are practically never adequate for the control of tetany. Calcium chloride given in divided doses totaling about 8 Gm. daily, or calcium gluconate or lactate, the latter two salts in approximately twice the dose of the chloride, should insure an adequate supply of calcium in the intestinal tract. However, some vitamin D preparation is required for promoting calcium absorption. Rarely is one of the usual vitamin D preparations sufficient. In recent years dihydrotachysterol (AT 10),[1] obtained by irradiation of ergosterol, has been found to be the most effective agent in the management of tetany. This material is given orally together with a calcium salt in amount sufficient to elevate the blood calcium level to within normal range. The amount required for this varies considerably. From 2 to 4 mg. of the crystalline material daily may be needed at the beginning of treatment when the serum calcium level is quite low. After a normal calcium level has been reached a maintenance dose of

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about 0.6 mg. daily will be required. Not only does AT 10 have the vitamin D effect of promoting calcium absorption from the intestinal tract, but also the ability to increase urinary phosphorus excretion to a considerable degree. Lowering the serum phosphorus causes a reciprocal rise in serum calcium. This latter property is believed to be the mechanism of parathormone action.

Over-dosage of AT 10 may result in hypercalcemia at the expense of the skeletal calcium, and if continued, may lead to the deposition of calcium salts in the soft tissues. The more immediate effects of hypercalcemia, especially when produced rapidly, are muscle weakness, vomiting and diarrhea. A convenient test by which a patient under treatment with AT 10 may regulate his calcium level has been suggested by Albright.[2] Equal amounts of urine and Sulkowitch's reagent are mixed; at normal serum calcium levels a slight milky precipitate forms. With higher levels a heavier precipitate appears and indicates the need for reducing the dosage of AT 10. If no precipitate appears an increase of the dose of AT 10 is indicated.

Parathyroid deficiency aside from causing tetany, is prone to result in the development of cataracts.[3] The probable mechanism for this ocular complication has been described by Clark.[4] The normal lens contains no calcium. Clark found that when enucleated animal eyes were immersed in solutions containing calcium the lens capsules slowly became permeable to it. After the lens had taken up calcium, exposure to ultraviolet radiation plus heating resulted in denaturation of the lens protein, i.e., cataract formation. It was shown further that the addition of minute amounts of parathyroid extract (parathormone) to the calcium solution made the lens entirely impervious to calcium. Thus it appears that a major function, probably *the* major function of the parathyroid hormone is to prevent the diffusion of calcium into cells. This is strongly supported by the finding that there is no increased calcium excretion following parathyroidectomy in animals and that the bodies of these animals contain no less calcium than do the controls. It would follow from this experimental work that lack of parathyroid hormone allows calcium to penetrate the lens capsule resulting in the formation of cataracts following exposure to ultraviolet light.

Case 1: Mrs. B. B., white, age 27, was admitted to Vanderbilt University Hospital in 1930 with the classical findings of thyrotoxicosis. Her basal metabolic rate was plus 77 per cent which upon administration of iodine fell to plus 46 per cent. She was then operated upon, the gland being difficult to remove as it partially encircled the trachea. A few days after operation a large hematoma developed in the wound and required packing. Later a secondary wound closure was required. She was not seen again until 1935 when she returned with mild symptoms of thyrotoxicosis. Over the next four years she had basal metabolic rates ranging from plus 8 per cent to plus 32 per cent and gave evidence of mild thyrotoxicosis during most of this time. It was noted during this period that several nodules appeared over her thyroid.

In 1939 she was readmitted to the hospital and two nodules of thyroid tissue were removed. The day after operation she complained of tingling of her extremities. The next day frank tetany appeared. The serum calcium level was 6.2 mg. per 100 cc. She was given intravenous injections of calcium gluconate with complete relief of tetany for periods of a few hours. She was also given intramuscularly 100 units of parathormone daily for eight days. This appeared to relieve the tetany to some extent. She was discharged from the hospital taking cod liver oil and calcium lactate by mouth. Three months after operation mild tetany was still present. No parathyroid tissue was found on examination of the excised thyroid gland.

She then disappeared for three years, returning in 1942 because of rheumatoid arthritis. Mild tetany had been present much of the time during her absence in spite of daily oral doses of calcium. The blood calcium level was 8.1 mg. at this time. She was given injections of gold thiosulfate over a period of several months for the arthritis.

In January of 1944 she complained of failing vision which had begun about three years before. Bilateral cataracts were present, resulting in total loss of vision in the right eye and greatly restricted vision in the left. On Jan. 11, 1944 a predominantly nuclear cataract was removed from her right eye. She was then referred to the medical clinic for further regulation of tetany. A positive Chvostek sign was elicited and her serum calcium was found to be 6.3 mg. per cent. Treatment was started with 2.5 mg.† of AT 10 twice daily together with calcium chloride by mouth. After two months on this medication the serum calcium had risen to 10.1 mg. per cent. The AT 10 was then decreased to 2.5 mg. daily. She has continued on this dosage and at no time has her serum calcium been less than 9 mg. per cent. She has remained free of tetany. She has regained vision to a considerable degree in the right eye. The vision in the left eye remains poor.

Case 2: G. M. W., colored female, 21 years old, was

† With crystallization of dihydrotachysterol 0.6 mg. is the therapeutic equivalent of 2.5 mg. of the less purified material available earlier.

admitted to this hospital in December 1939 with typical thyrotoxicosis. There was a high degree of exophthalmos. After administration of iodine and phenobarbital for 12 days a subtotal thyroidectomy was performed under local anesthesia. The pulse rate and temperature increased greatly late on the day of operation. It was noted at this time that she was hoarse and inspection of the vocal cords revealed them to be in the adductor position. Respiratory embarrassment became so great that a tracheotomy was performed. Carpopedal spasm was then noted for the first time. This was quickly relieved by an intravenous injection of 10 cc. of 10 per cent calcium gluconate solution. The tracheotomy tube was removed after 11 days at which time abduction of both vocal cords was observed. Severe tetany persisted and required frequent injections of calcium intravenously. By the 24th postoperative day the tetany had become much less severe and her vocal cords were described as moving normally.

Two weeks before thyroidectomy this patient's serum calcium was 10.6 mg. per cent. On the second day following operation it had fallen to 6.7 mg. per cent. Daily calcium determinations during the postoperative period gave essentially the same values, although the tetany did not exactly parallel the calcium levels. No parathyroid tissue was found with the thyroid tissue removed.

The patient was discharged from the hospital to the outpatient department with instructions to take oral calcium and cod liver oil. She continued to have mild tetany. Approximately one year after thyroidectomy because of visual difficulties she was fitted with glasses which she wore continuously. She was rarely free of generalized aching and a sensation of muscle tightness, and evidence of latent tetany was elicited on each of numerous visits to the outpatient department. She became pregnant and was delivered in November 1941, this being her second child, the first having been born before the development of thyrotoxicosis. There was some increase in the severity of tetany during the second pregnancy. Following delivery she nursed the baby for approximately two months. During the period of lactation tetany became quite severe causing her to come to the hospital emergency room on several occasions for intravenous injections of calcium. She was advised to wean her baby. She did this and experienced some improvement, but control of the tetany was less effective than before pregnancy. In March 1942 the administration of AT 10 was begun and has been continued to the present. At times she has been kept reasonably free of tetany with 2.5 mg. of AT 10 every second day; at other times a daily dose of 2.5 mg. has been required. She has had two subsequent pregnancies each of which necessitated an increase in the dose of AT 10. Following both deliveries tetany increased in spite of the fact that she was not allowed to nurse the babies at breast. At other times the serum calcium levels have been maintained at approximately normal values.

DISCUSSION

Several points which deserve emphasis are illustrated by these case reports. In neither patient was tetany controlled by the administration of large amounts of calcium by mouth together with cod liver oil. Only after substituting AT 10 for cod liver oil were the calcium levels raised to normal and tetany controlled. In Case 2 it appears very likely that the extreme respiratory difficulty was due to severe tetany, and had this been recognized tracheotomy would not have been required. As mentioned previously the vocal cords assume a closed position (that of abductor paralysis) both in severe tetany, in which case it is caused by adductor spasm, and in recurrent laryngeal nerve paralysis causing abductor paralysis. Hence inspection of the cords does not help to differentiate between these two possible complications of thyroidectomy. When stridor is due to tetany the general examination usually reveals other signs of muscle hyperexcitability. Moreover, the vocal cord involvement following nerve injury usually becomes apparent while the patient is on the operating table, while that associated with hypoparathyroidism develops a number of hours later.

The fact that the patient who was provided glasses did not develop cataracts, while the patient without glasses did develop this complication suggests, an interesting possibility. The experimental work of Clark, described above, suggests that the protection of the eyes from ultraviolet rays which was afforded by the optical lenses, may have prevented the development of cataracts in this patient.

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The frequency of mild (and severe) head injuries is great and the practitioner must be familiar with such complications or sequela as subdural hematoma discussed in this paper.

Diagnostic Aspects of Subdural Hematoma*

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Chronic subdural hematoma is the most frequent late surgical complication of head injury. It is more common than is generally realized, but unfortunately is still frequently overlooked. However, it has been the subject of great interest in the past and there is an extensive literature on the subject.

Groff and Grant[1] prepared an excellent collective review in 1912 with a summary of the literature to that date. They classified the causes under the headings "spontaneous" and "traumatic." Under each of these headings primary and secondary causes were listed. Primary spontaneous causes were infectious and neoplastic; secondary spontaneous causes were the predisposing factors of systemic disease, alcoholism, arteriosclerosis and blood dyscrasias. Trauma was described as a primary cause and also as a secondary or precipitating cause in the presence of one of the predisposing factors listed under spontaneous causes

In the recent literature the trend has been to consider trauma as the most important etiologic factor. The normal anatomy of the cerebral veins has long been recognized as important in the production of subdural hemorrhage. The term "bridging veins" may be applied to the veins that cross the subdural space to the dural venous sinuses and also to the veins that cross the subdural space traveling between the arachnoid and dura, but emptying directly into any sinus. The first group includes the superior cerebral veins, the inferior cerebral veins that enter the sphenoparietal sinus, and the veins that enter the lateral sinus from the posterior or inferior surface of the temporal lobe. Other veins cross from the cerebral arachnoid of the convexity of the hemisphere in the dura at a distance of 1 to 4 cm. from the superior longitudinal sinus, traverse the subdural space from the arachnoid of the base of the temporal lobe to the dura of the middle fossa and to the tentorium cerebelli, cross from the tip of the temporal lobe to the dura over the sphenoid bone, or enter the dura from the lateral convexity of the hemisphere at any point. All of these veins are familiar to the neurosurgeon because they limit his manipulations when he explores the subdural space.

It is obvious that displacement of the brain in the intracranial cavity, especially in the longitudinal axis, may tear these veins as they cross the subdural space and may produce primary subdural hemorrhage. Beginning with Trotter,[2] many authors have recognized this as the probable initial step in the production of a subdural hematoma. However, experimental proof of this has been lacking until Sheldon, Pudenz and Restarski[3] demonstrated experimentally subdural ("sublucite") venous bleeding following parietal subconcussive blows in monkeys in whom the convex portion of the skull had been replaced by a transparent Lucite calvarium. This experimental demonstration supports the clinical supposition that an initial hemorrhage into the subdural space is the first stage in the development of a subdural hematoma. Such hemorrhage is most apt to occur from superior cerebral veins but often occurs from other groups, so that while the majority of traumatic subdural hematomas occur over the convexity of the cerebral hemisphere they are found inferiorly in the temporal region both anteriorly and posteriorly, occasionally beneath the frontal and temporal lobes and even in bizarre locations, such as between the hemispheres (Aring and Evans)[4] or beneath the tentorium cerebelli (Munro).[5]

In a previous paper[6] a series of 100 consecutive cases of subdural hematoma that were operated on has been reported. A definite history of antecedent trauma to the head was obtained in 96 of these cases The time between the injury and the operation in this series ranged from a few hours to six months. Injuries occurring more than six months *before* the patient is first seen with symptoms of a subdural hematoma, are probably not the cause of the hematoma. In fact injuries occurring more than three months before the onset of symptoms must be regarded with suspicion.

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The differentiation between acute and chronic forms of subdural hematoma is important from both the standpoints of treatment and prognosis. The most convenient clinical classification is on the basis of elapsed time between the injury and the operation on the patient. In the series previously referred to all cases in which this time interval was one week or longer were considered as cases of chronic subdural hematoma; cases which the interval was less than one week were classified as acute or subacute. In this paper, the diagnostic aspects of chronic subdural hematoma only will be discussed.

Men and women are probably equally susceptible to subdural hematomas, but the greater frequency of head injury in males is reflected in the much greater frequency of subdural hematoma in that sex. Subdural hematoma occurs at any age but is rare between infancy and young adulthood. The fourth, fifth and sixth decades of life provide the most cases.

The most common finding in subdural hematoma is some degree of mental disturbance. This may range from mild personality disturbance to stupor or coma. The mental picture may fluctuate greatly but worsens with the passage of time. Confusion and disorientation with progress to stupor or coma are frequent. Drowsiness and slowing of mental processes are often seen. Indifference to the situation with lack of insight are also often a prominent feature. Simulation of one of the organic psychoses is infrequent, but occasionally occurs.

Weakness or paralysis of one side of the body with abnormal or pathologic reflexes is usually contralateral to the hematoma; occasionally the contralateral crus cerebri is pressed against the free edge of the incisura tentorii, and hemiparesis and pyramidal tract signs are thus produced homolateral to the clot. This plus the fact that subdural hematoma is bilateral in 15 to 20 per cent of cases makes it advisable to carry out bilateral exploration in all cases of suspect subdural hematoma. Progressive hemiparesis or signs of unilateral involvement of the pyramidal tract after a head injury are strong presumptive evidence of a subdural hematoma, but these findings may of course be produced by localized injury to the brain.

Headache commonly occurs, and as in intracranial pressure due to other causes, may be associated with nausea and vomiting. Unilateral dilation of the pupil was recorded in nearly half of the author's cases. It is generally homolateral to the lesion but in about ten per cent of cases was contralateral to the hematoma. This is thus not only a frequent sign of a developing hematoma but is also a valuable localizing sign. When it is contralateral to the hematoma the possibility exists of injury to the brain on the side of the dilated pupil.

Papilledema will be seen in one-third to one-half of the cases. This finding developing after a head injury is very strong presumptive evidence of a chronic subdural hematoma. However, a transitory papilledema may follow head injury without subdural hematoma. Usually these cases have no subjective symptoms and eventually the elevation of the optic disks always disappears. The cause of such transitory papilledema is not clear.

Convulsive seizures occur in about 30 per cent of cases. This is about the frequency usually reported for tumors of the cerebral hemisphere. When seizures are unilateral they have great localizing value. Convulsions occurring a few days or longer after a head injury are suggestive of a possible subdural hematoma; they may of course be due to localized cerebral contusion or edema. Occasional bradycardia with a pulse rate below 60 is seen in about 30 per cent of the cases. It is seldom persistent but tends to be recurrent. As it is usually noted only by review of the hospital chart over a period of several days it is undoubtedly often overlooked in patients who have been in the hospital only a short time.

Examination of the spinal fluid is very important in cases of suspected subdural hematoma. In a high percentage of cases (70 to 80) the fluid will be found to be xanthochromic. Clear spinal fluid does not rule out or even made unlikely, the presence of a subdural hematoma, but xanthochromic spinal fluid usually indicates such a diagnosis. However, the finding of xanthochromic spinal fluid must be disregarded if the examination is made within two weeks after a head injury, as in such cases it may be the result of subarachnoid hemorrhage suffered at the time of the injury. Observations on a large number of cases of traumatic subarachnoid hemorrhage indicate that the spinal fluid will be normally clear within 12 to 14 days after a cerebral injury unless there is a developing subdural hematoma.

The discovery of xanthochromic spinal fluid in a patient suffering from organic cerebral disease without a history of head injury suggests the possibility of subdural hematoma. Recent spontaneous subarachnoid hemorrhage or cerebral neoplasm are also to be considered. However, in several patients admitted to a hospital in stupor or coma without an adequate history, the finding of xanthochromic spinal fluid has led to the presumptive diagnosis of subdural hematoma with verification by surgical exploration.

The value of air studies is debatable. Davidoff and Dyke [7] were of the opinion that the encephalogram

(spinal air) is of diagnostic importance. Others (e.g., Bull) [8] have emphasized the difficulties of diagnosis by air studies. Ventriculography has often led directly to the correct diagnosis for when the surgeon made burr holes in the skull for the injection of air, the subdural hematoma was encountered.

From a diagnostic standpoint chronic subdural hematoma can be divided into two general types. In the first type, subjective symptoms are present from the time of a head injury which may be either mild or severe. In these patients the relationship of the injury to the patient's symptoms is evident; the only question is whether or not a subdural hematoma exists. The persistence or development of some combination of the symptoms we have described should lead the physician to the realization that the patient may have a subdural hematoma with consequent exploration.

In another group of patients the injury was trivial, and had been forgotten or was not known to friends or relatives. In some patients in this group, the improvement of memory after drainage of the hematoma has resulted in the recollection of the causative injury. The patient had considered the injury inconsequential and had later failed to recall it on questioning because of the mental impairment produced by the hematoma. These patients are suspected of some other cerebral organic disease as brain tumor, cerebral vascular disease, an encephalopathy, or encephalitis. If the patient is first seen in coma, uremia or diabetes may be suspected. As a matter of fact in several of the author's cases one of these conditions has complicated subdural hematoma. This is most likely to occur in the elderly patients. The alert clinician will search for other causes of stupor or coma when adequate treatment of uremia or diabetes does not result in satisfactory improvement.

The value of diagnostic spinal puncture in the differential diagnosis of coma must be emphasized. As already stated this procedure in the comatose patient may promptly lead to the correct diagnosis. Even if the fluid is not xanthochromic the total protein value may be significantly increased and this at least will indicate organic cerebral disease.

Fluctuation of symptoms, especially of the state of consciousness, is often seen, and at times is so dramatic as to lead to the correct diagnosis by the experienced physician. No other space-occupying lesion in the author's experience so often permits wide fluctuation of symptoms. On the neurosurgical service at the Cook County Hospital where many patients with craniocerebral injury are cared for, patients in group one have frequently been observed in the hospital for several weeks after their injury before the diagnosis of subdural hematoma could be made. We have learned to suspect this condition wherever fluctuation in the patient's symptoms occurs. The patient whose mental status or objective neurologic signs fluctuate after a head injury very likely has a subdural hematoma.

At times the fluctuation may be dramatic so that a patient may rally from coma or even apparent impending death to relative normality. The improvement is of course only temporary and unless the diagnosis is made the patient again becomes worse and finally dies

The most important factor in the diagnosis of subdural hematoma is the alertness of the clinician. He must recognize not only that the patient with a history of head injury may have a subdural hematoma but also that any patient with signs and symptoms of cerebral disease may have this condition. He must especially consider that possibility when confronted with "stroke" or "mental disease" or with a patient in coma. The manifestations of subdural hematoma are protean and there is no constant factor, except surgical exploration, that will establish the diagnosis Fortunately bilateral exploratory burr holes can be made under local anesthesia, in even the seriously ill patient, without undue risk and without significantly decreasing the patient's chances for recovery if a hematoma is not found. There should therefore be no hesitancy in exploration of the patient in whom this condition is suspected.

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The management of lipoid nephrosis is surrounded by controversy and the difficulties of evaluating therapeutic procedures in a disease of cyclic nature. The author considers all phases in the management of these patients and offers well-balanced suggestions for treatment.

Treatment of Lipoid Nephrosis*

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Lipoid nephrosis is a disease of childhood characterized by proteinuria, hypoproteinemia, generalized edema with or without ascites and hydrothorax, hyperlipemia, decalcification of bones,[7] negative nitrogen balance, and acceleration of the erythrocytic sedimentation rate. Hematuria is usually absent, but occasionally transitory microscopic hematuria may be detected. Azotemia, if present, is slight and occurs only during periods of oliguria. The blood pressure is usually not elevated but may be elevated during periods of oliguria. The cause of nephrosis remains unsolved. Based on the clinical, pathologic, and laboratory findings, there are several theories attempting to explain the cause and the sequence of events leading to the nephrotic syndrome.

Various mortality and recovery rates are stated in the literature. Aldrich[1] writes of a 50-50 chance of recovery. Schwarz and his co-workers[19] reported that 25 per cent of their patients recovered completely. Tappan[22] reported a mortality rate of 51 per cent; Rubin,[17] 50 per cent; and Heymann and Startzman,[11] 15 to 20 per cent. Chronic nephritis sometimes has a nephrotic phase, but it was chronic nephritis from the beginning, though a little time may pass before the correct diagnosis can be made. It is the author's opinion that the diagnosis "nephrosis complicated by chronic nephritis" is the result of the clinician's denial that his clinical diagnosis was wrong and represents a compromise between him and the pathologist. Some of the high mortality rates may be accounted for by the inclusion of deaths due to "nephrosis complicated by chronic nephritis" in the mortality rates. It is our impression that uncomplicated nephrosis in childhood is rarely fatal.

The treatment of nephrosis continues to be symptomatic; one important phase is directed at the prevention and treatment of intercurrent infections, which are responsible for most, if not all, of the deaths in nephrosis. Controversial theories have led to numerous modes of therapy. Interpretation of results has been difficult because of the cyclic nature of the disease and the concomitant use of several measures directed toward obtaining the same result.

GENERAL CARE

The care of a child with nephrosis presents certain disadvantages in a hospital, namely, the increased exposure to infections and the lack of parental care. Nevertheless, hospital care presents numerous advantages over home care—advantages which outweigh the disadvantages—and, furthermore, the disadvantages can be corrected to a great extent.

The patient should be kept in a single room or in a larger room with several other children with nephrosis. Visiting hours should be shortened to a minimum, and all those entering the room should be masked in an effort to minimize the incidence of upper respiratory infections. It is our practice to isolate a child with an intercurrent infection from the other children.

All relatives are requested to make as few visits as possible in order to facilitate the establishment of rapport between the attending staff and the child. The relatives are told at the outset of the chronicity of the child's illness.

The patient's activities should be unlimited except during periods of marked edema and intercurrent infections, during which he should be at bed rest. Recreational activities should be provided and supervised by a competent and understanding occupational therapist or nurse, and educational guidance should be provided by a teacher.

Constant nursing care is of utmost importance. Ideally, one nurse should be assigned to the care of the patient's physical and emotional needs—one who understands the cyclic nature and the chronicity of the disease and one who can substitute adequately as a mother.

When a child with nephrosis cannot be hospitalized because of financial and other reasons, another plan is necessary. A plan which has been found to be satisfactory is to allow the child to be at home and to hospitalize him only during periods of crisis and severe intercurrent infection and for procedures such as ab-

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dominal paracentesis and thoracentesis. Follow-up examinations can be done on an outpatient basis.

THE NEPHROTIC DIET

Of any single measure in the medical management of a nephrotic child, emphasis should be placed on his diet. Practically all who have had their disease for several months are malnourished and appear well-nourished under the mask of generalized edema. We prescribe a high-protein, high-carbohydrate, low-fat, low-salt diet given five times daily. The food is prepared as attractively as possible. The protein offered varies between 3 and 4 Gm. to a kilogram of non-edematous body weight each day. Ample carbohydrate is provided to meet or exceed the daily energy allowances based on age as recommended by the Food and Nutrition Board of the National Research Council. The diet is made low in fat because of the anorexic effect of fat and not to correct the hyperlipemia. The hyperlipemia continues in spite of a low fat intake. The term "salt-free" should be discarded, inasmuch as a high protein diet necessitates the giving of salt bound with protein. By a low-salt diet is meant a diet without additional salt. In an effort to decrease salt intake, dialyzed milk has been used to replace skimmed milk. Those patients who have been unable to eat a high-protein diet without additional salt have been allowed to have a reasonable amount of salt added to their food. No ill-effects have been experienced from this procedure.

The question of limiting or not limiting fluid intake has not been answered scientifically. It is our practice not to limit oral fluids but to allow the patient to take as much as he wants. Spontaneous diuresis has occurred in many of our patients in spite of unlimited fluid intake. For the management of edema, Schemm and others [1, 16, 18] have advocated the use of liberal fluids, the acidification of fluids to mobilize the sodium ion from the alkaline ash media of the tissue interspaces, the use of acid-ash drugs, and the restriction of sodium chloride to about 1 to 2 Gm. daily. Their clinical results have been encouraging.

One to two times the daily minimum requirements of vitamins should be provided. Our experience with the use of choline, based on experimental evidence that it is necessary for fat metabolism, and with the use of pyridoxine, based on experimental evidence that it is necessary for protein metabolism, has been disappointing.

Farr and McFadyen [11] demonstrated that a chronic deficit in blood amino acids often accompanied the disease. They also demonstrated that, after a heavy protein meal, there is evidence that no delay exists in protein digestion or absorption. Unpublished data in our own experience confirm their findings. The use of amino acids orally offers a means of providing the nephrotic patient with extra amounts of these protein-building substances. The use of amino acids intravenously will be discussed in more detail later.

ROLE OF BLOOD, BLOOD FRACTIONS AND RELATED SUBSTANCES

Anemia of some degree occurs in practically every nephrotic child and invariably is of the microcytic hypochromic type. The relative anemia seen during periods of rapid shifts in body fluids should not be confounded with true anemia. Iron compounds orally or intravenously and liver injections have been ineffective in correcting anemia; transfusions of whole blood or concentrated red cells are indicated in correcting the anemia.

In the past we have given patients numerous transfusions of fresh and lyophile concentrated or unconcentrated plasma with the intention of correcting the hypoproteinemia and inducing diuresis. Because of the cyclic nature of the disease, our few satisfactory results have remained equivocal in respect to their cause. At present, we are using plasma, not as an agent to correct hypoproteinemia, but as a source of protein during periods of anorexia, vomiting and diarrhea. Aldrich and Boyle [2] reported good results using concentrated human blood serum. The over-all experience with plasma or serum has been discouraging.

More recently, the use of concentrated low-salt, human serum albumin has received much attention in investigative studies as an agent for correcting hypoproteinemia and inducing diuresis. Twenty-five grams of this substance are osmotically equivalent to 500 cc. of plasma. Published [5] and unpublished reports throughout the country vary in enthusiasm about its effect in correcting hypoproteinemia, but the consensus is that it is a relatively safe and effective but expensive diuretic.

The question remains: are these proteins, given intravenously, metabolized, are they stored in tissues as foreign proteins, or are they excreted? We know that urinary output of protein increases with the intravenous administration of plasma or albumin. By nitrogen retention studies, these patients can be shown to be in positive nitrogen balance during the few days of the balance study. Further studies are indicated.

Hartmann and his co-workers [12] in 1933 advocated the use of acacia intravenously as a means of treating children with nephrosis. Dick and his co-workers [6] in

1935 and Jackson and Frayser [15] in 1938 and others, reported ill-effects of acacia. The outstanding features after intravenous administration of acacia were as follows: The presence of enlarged and tender livers; the finding of acacia in the liver, bone marrow, lymph nodes, lungs, kidneys, muscles and spleen; a further decrease in serum proteins with delay in protein regeneration after stopping the use of acacia; the development of a marked anemia with slow regeneration of red cells and hemoglobin after stopping the use of acacia. Particles of acacia are taken up by the phagocytic cells of the reticuloendothelial system and stored as foreign bodies in the liver and elsewhere. As a result of storage in the liver there is decreased liver function superimposed on an already over-burdened liver. In recent years the use of acacia is again being advocated. We have not used acacia since 1935 and strongly recommend against its use.

We have avoided the use of gelatin solutions intravenously for fear of obtaining complications similar to those experienced with acacia. Some workers have reported satisfactory results with the use of gelatin, but on the whole, results have been discouraging.

Recently, Strumia and his co-workers [20, 21] reported on the use of globin and its diuretic effect in chronic nephritis. Twenty-four grams of globin are osmotically equivalent to 600 cc. of plasma. Their report is encouraging. The author knows of no cases of nephrosis treated with globin.

INTRAVENOUS TECHNIC

Because of the numerous solutions given intravenously over a fairly long period of time and because of the numerous laboratory determinations on blood performed in following the patient's course, emphasis on intravenous technic is in order. Venesections should never be performed except in emergencies. To a pediatrician, there is probably nothing more disconcerting than to receive under his care a patient who had had numerous venesections. Because of the possibility of developing osteomyelitis, bone marrow infusions should not be performed except in emergencies. Veins most commonly used for drawing blood are the external and internal jugular veins and the veins in the antecubital fossa. In very young children, blood may be drawn from scalp veins, the longitudinal sinus, and the femoral veins. To permit the administration of blood, plasma, albumin, amino acids and other solutions, the great saphenous vein anterior to the medial malleolus, the external jugular veins and veins over the abdomen, chest, antecubital fossa, wrist, dorsum of the hand, dorsum of the foot, and scalp may be used. For younger children, we have used 25-gauge needles for administering all kinds of fluids and drugs, including whole blood and albumin, rarely encountering plugged needles. Plugged needles are opened by forcing a small amount of saline solution through the needle with a syringe. In older children, a 25-gauge needle is used for administering plasma, amino acids, and other less viscid fluids and a 22- or 20-gauge needle for administering blood, concentrated plasma, and albumin. A small-gauge needle is used in most instances in order to save as many veins as possible for repeated use. To prevent the needle from slipping out of a vein due to traction on the needle by the weight of the heavy tube customarily used in an intravenous set, we attach a light, small-caliber rubber tube between the needle and the heavy tube.

ROLE OF OTHER DIURETICS

Diuretics such as urea, ammonium chloride, mercurials, hypertonic sucrose, and xanthines are usually ineffective in inducing diuresis. Furthermore, mercurials and hypertonic sucrose are harmful to the kidney tubules and are contraindicated during periods of oliguria and anuria. It is our clinical impression, nevertheless, that during periods of spontaneous diuresis these drugs are harmless and probably helpful in increasing urinary excretion early in nephrosis. There is no experimental proof for this last statement, however. Since using concentrated human serum albumin, we have not used any of these diuretics.

ROLE OF THYROID PREPARATIONS

A low basal metabolic rate and hypercholesterolemia are constant findings in nephrosis and in hypothyroidism. In 1917, Eppinger [8] advocated the use of thyroid preparations, and since then many physicians have been using them. Heyman and Clark [13] demonstrated experimentally that the kidneys of dogs, cats, rats, and monkeys are involved in a mechanism which influences blood lipid concentration, and they advanced the hypothesis that the hyperlipemia found in cases of nephrosis is related in some way to the renal tubular lesion. The low basal metabolic rate in nephrosis is presumably on the basis of malnutrition. We have used amazingly high doses of thyroid to the point of inducing symptoms and signs of overdosage with thoroughly disappointing results. We have discontinued using thyroid.

FEVER THERAPY

Based on the clinical observation that many nephrotic children recover after a febrile episode, typhoid vaccine and other foreign proteins have been

tried. For some reason, children with nephrosis do not develop high fever in many instances after intravenous administration of foreign proteins even after high doses. Results from use of foreign proteins have been discouraging. We have vaccinated our patients repeatedly with cowpox vaccine, hoping to obtain a febrile response, but our results have been discouraging.

ABDOMINAL PARACENTESIS AND THORACENTESIS

The indications for abdominal paracentesis are: A tight, protruding abdomen associated with anorexia, abdominal pain, oliguria, nausea, and vomiting; a rapid decrease of edema of the extremities with rapidly increasing ascites; coarse râles at both bases of the lungs associated with marked ascites; and early hydrothorax demonstrable by physical signs or radiographically.

The technic of paracentesis is simple. The patient voids or is catheterized a few minutes prior to the procedure. With the patient held in a sitting position, the skin of the lower half of the abdomen is painted with tincture of iodine and 70 per cent alcohol. The operator, wearing sterile gloves, drapes the operative site—half of the distance between the navel and symphysis pubis. One to two per cent procaine is injected into the skin to make a wheal. A small stab wound, large enough to allow a trocar to pass through, is made. With firm pressure, the trocar is pushed into the abdominal cavity. A large container collects the fluid as it flows out of the trocar through a rubber tube. Several changes in the direction of the trocar will frequently yield more fluid. The wound is covered with a heavy sterile absorbent dressing. No sutures are necessary. Frequently, fluid will drain for several days, and this occurrence should cause no alarm. We follow this procedure with a course of penicillin parenterally for 24 hours. In those patients requiring numerous paracenteses, we have entered the abdominal cavity lateral to or above or below the usual site without encountering complications. In those having had numerous paracenteses and when there is difficulty in passing a trocar because of fibrosis of the abdominal wall, we have used an ordinary 18-gauge needle to which a rubber tubing is attached.

The indications for thoracentesis are: Hydrothorax not relieved by abdominal paracentesis; hydrothorax occurring suddenly and massively, causing respiratory distress; and unilateral and bilateral hydrothorax occurring at short intervals.

The best site for thoracentesis is the first or second interspace immediately inferior to the inferior angle of the scapula. The skin is prepared as for paracentesis. A 19- or 18-gauge needle attached to a syringe is introduced over the superior edge of the rib to avoid intercostal vessels and nerves. A three-way stopcock facilitates the removal of fluid. We follow this procedure with a 24-hour course of penicillin parenterally.

INTERCURRENT INFECTION AND FOCI OF INFECTIONS

Pneumococci, staphylococci, and streptococci are the most common secondary invaders. Pneumococci have been cultured from the nose and throat so often that some workers have theorized that they are in some way related to the cause of nephrosis. Before the era of sulfonamides and antibiotics, peritonitis, septicemia, and pneumonia were common causes of death. Since the advent of these drugs, the mortality rate from these infections has dropped considerably. Dosages of these drugs are not different from those used in other children with infections by the same organisms.

Paradoxically, almost every type of intercurrent infection at one time or another has been reported to have favorably modified the course of, or cured a child with nephrosis. Of these infections, measles appears to be the most outstanding. Blumberg and Cassaday[3] recently stated that infection with measles had been more effective in causing a remission of nephrosis than any therapeutic agent that they had used. There is no doubt that these remarkable remissions have occurred, for we have seen them occur in our cases. Nevertheless, some of the patients have died from complications during or after their infection with measles. It is the author's opinion that inoculation with measles as a therapeutic agent is not justified even when the disease is modified with gamma globulin.

Upper respiratory infections occur rather frequently and easily. The mild infections should be left untreated. The more severe infections should be treated adequately with chemotherapeutic agents and antibiotics.

Diarrhea occurs fairly frequently, especially during periods of increasing edema and oliguria. Whether or not diarrhea is a compensatory mechanism whereby edema fluid is removed is a question open to speculation. As a safeguard, we have isolated every patient developing diarrhea, although we have yet to culture pathogenic organisms from the stools. Treatment is usually unnecessary except in those with specific diarrhea.

The nurse should see that bedsores and skin infec-

tions, especially around an edematous scrotum or vulva, are prevented or treated early if they occur. Minor infections have ultimately been responsible for the death of some of these patients.

The removal of foci of infection has received great emphasis in the past. We have been treating foci of infection without anticipating any improvement of the disease but only as a step toward improving the general condition of the patient and preventing the progress of a focus into something of major concern.

MANAGEMENT OF THE NEPHROTIC CRISIS

The nephrotic crisis is characterized by sudden fever, anorexia, nausea and vomiting, chest and abdominal pains, erysipeloid lesions, oliguria, increasing edema and prostration. Farr [9] redefined a nephrotic crisis: A nephrotic crisis is said to exist whenever the plasma amino acid concentration falls below the critical level of 2.5 mg. for each 100 cc. and to have ceased when the value has risen above this figure. Although in a great number of instances no infectious agent can be demonstrated, we treat a crisis as if it were an intercurrent infection using a specific drug whenever a causative agent is isolated and either a sulfonamide or penicillin in a crisis where no cause is found. Supportive treatment consists of the intravenous administration of 5 per cent amino acids in 5 per cent glucose several times daily,[10, 11] blood transfusions if indicated, paracentesis and thoracentesis if indicated, and the use of an oxygen tent if indicated by cyanosis or respiratory distress. One of our patients recently became practically anuric during a crisis, edema developed rapidly, and ascites and hydrothorax became marked. Suddenly, convulsions occurred and the patient became comatose. Cerebral edema was diagnosed. Within the course of two hours, an abdominal paracentesis, bilateral thoracentesis, and a lumbar puncture were performed. On the next day he was sitting up in bed, talking and feeding himself.

During periods of crisis and marked edema, subcutaneous drainage of fluid by skin incision is very rarely, if ever, necessary. The procedure is simple, but the possibility of infection is a strong contraindication.

Frequently, a nephrotic crisis will simulate acute appendicitis or intestinal obstruction or some other acute surgical condition. Conservative management of all crises simulating these complications should be followed until a diagnosis is fairly certain.

Spontaneous recoveries or improvements have occurred after nephrotic crises. Numerous deaths have occurred during crises encountered in various clinics throughout the country. The child in a crisis deserves every supportive measure for his welfare to carry him through the few days of a crisis.

SUMMARY

The general care; the diet; the use of blood, blood fractions, and amino acids; intravenous technic; indications and technics for abdominal paracentesis and hydrothorax; the role and management of intercurrent infection; and the management of crises have been emphasized in the treatment of lipoid nephrosis. The intravenous use of acacia is definitely contraindicated and gelatin solutions are probably contraindicated. Mercurial diuretics and hypertonic sucrose are dangerous during periods of oliguria. Thyroid preparations and probably foreign proteins have no place in the treatment of nephrosis. At the present time, there is no safe and sure way of shortening the course of or curing the disease. The treatment continues to be symptomatic and includes prevention and treatment of intercurrent infections.

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BOOK REVIEWS - - -

PRINCIPLES AND PRACTICE OF MEDICINE. By Henry A. Christian, M.D. Ed. 16, 1700 pages. New York, Appleton-Century, 1947. Price $10.00.

To one who was "raised" on Osler's *Principles and Practice,* it comes as somewhat of a shock to receive the newest edition of *Principles and Practice* without the name Osler on the book's cover or spine. This should not be construed as a criticism of Dr. Christian, the present author, who brings to his task many of the special qualities of his predecessor, qualities which made possible the distinctive character of the book originally and make it possible for the present author to maintain that character, and who is one of the few remaining internists with courage enough, knowledge enough and ability enough to write singlehanded such a text. The change does, however, mark the end of an epoch, the passing of a period, and cannot fail to remind many readers of that fact.

The present, 16th edition, published some three years after the 15th, covers a period in which many advances, and there were many, failed to appear in current periodicals because of the war. They include the evaluation and delimitation of such agents as the sulfonamides and the various antibiotics, with clarifications of such matters as dosage, routes of administration and the like. New developments in the etiology and epidemiology of many of the infectious diseases have occurred.

A few new diseases have been recognized and much more has been learned about many which were strange and unfamiliar only a short time ago.

Many of these advances are included in this edition which runs to 1,539, plus, pages. As in recent editions, the book begins with a discussion of the psychosomatic disorders instead of the typhoid fever of the Oslerian days, in itself a commentary on the changing aspect of medicine. It then progresses through the diseases caused by various living agents, to those due to physical agents, intoxications, the nutritional deficiencies and metabolic disorders. Diseases of the various systems and organs follow and the book closes with the organic diseases of the nervous system as do most texts on medicine. Sections which have been added, or added to, include histoplasmosis, pretibial fever, schistosomiasis, infectious viral hepatitis, Whipple's disease, Wolff-Parkinson-White syndrome, congenital heart disease and Edgeworth's disease, among others.

Among the few and rather minor inadequacies noted are the discussion of herpetic stomatitis, the use of "BAL" in the treatment of arsenical and mercurial poisoning, sprue, and nitrogen metabolism in injury and disease.

Throughout these appear the personal experience, judgment and, shall we say, bias of the author. This is as it should be in a book by a single author, and to this the book owes much of its peculiar virtue.

The size of the book and its thickness make it a somewhat awkward volume to handle. The rather poor paper is presumably a result of the paper shortage. In the reviewer's copy there are several irregularities in pagination and some 55 pages numbered 515, ending with a blank page. Similar irregularities appear throughout the book.

Besides the preface to this edition, the Preface to the 14th semi-centenial edition is reprinted and the Preface to the first. A very interesting feature is a "History of Medicine (1892–1947)" as told in the 16th edition by Dr. James Z. Carr. Nothing will serve better to illustrate the changes which have occurred in 55 years covered by this book.

As far as the whole of internal medicine can be covered in a single volume by a single author, this book

(Please turn to Page 182)

Epidemics of ringworm of the scalp have been reported in past years from the larger population centers. This report deals with an epidemic in a small community with suggestions for control under such circumstances.

Review of a Minor Epidemic of Ringworm of the Scalp*

FRANCIS W. LYNCH, M.D. AND ISADORE FISHER, M.D.

ST. PAUL, MINNESOTA

Until recently smaller communities have had no experience with epidemic ringworm of the scalp, and for this reason it is thought worthwhile to record the manner in which a small epidemic was brought under control in New Richmond, Wisconsin, a city of about 3,000 inhabitants. In recent years a nationwide epidemic has occurred and there have been several reports of the manner in which larger cities have met the new problem. High prevalence of ringworm of the scalp occurred in Hagerstown, Maryland (pop. 32,491 in 1940), affording an opportunity for the United States Public Health Service to test some of the new ideas of control.[1] It is evident that smaller communities can learn from that project but cannot afford the methods employed there: 15 months' service of an officer from the dermatoses section of the United States Public Health Service and the training of a nurse and nurse's aides for each of the seven treatment centers. In St. Paul, Minnesota (pop. 287,730 in 1940), an epidemic of similar proportions was controlled by one or two hours' weekly service of a dermatologist (actually the alternation of two dermatologists), two nurses and a secretary at one treatment center, and in addition, the co-operation of the nurses regularly employed by the Board of Health and the Department of Education, who continued to perform their usual duties while carrying on continuous surveys of the school population, using Wood's light.[2]

Little has been written about the minor satellite epidemics which have occurred in smaller communities. The relative importance of these smaller epidemics is partially due to the difficulty in obtaining adequate therapy and supervision, and partially to the fairly large number of infected persons. In a period of 15 months there were 88 reported instances of infection in Minnesota outside St. Paul and Minneapolis.[3] For geographic reasons many satellite cases must also have occurred in Wisconsin, but figures are unavailable because the disease is not reportable there. It is likely that many small cities will be forced to meet such a problem and it is therefore thought worthwhile to record the success of relatively inexpensive methods employed in New Richmond, Wisconsin, the center of a trading population of about 8,000, lying in an agricultural area 43 miles from St. Paul. The community became aroused when the recognition of several cases made evident that a minor epidemic had begun. Dermatologic consultation was arranged for and the next step was a complete survey of the approximately 450 students of both private and parochial elementary schools by an experienced nurse using Wood's light. After the initial survey of the students in November 1945, it was thought best to segregate the infected children from both the public and the parochial schools, placing them in a single class room in a community building separate from the school. This class was continued throughout that school year. The infected children were required to wear caps at all times. All diagnoses were confirmed by fluorescence in Wood's light and by cultural studies which demonstrated M. audouini in each case. The rapid success of the control methods was entirely due to the absolute co-operation between the physicians of the community (who agreed not to accept infected children for treatment), the medical health officer, the superintendent of schools and the parent-teacher groups of the public and parochial schools. The methods for control were outlined by a trained dermatologist who spent about two hours in the city; a dermatologist-in-training spent four hours there, assisted by a nurse experienced with Wood's light, initiation of cultures and manual epilation. During this time the regular school nurse acquired sufficient training to continue in complete local charge of the problem. Radiotherapy, subsequent epilation with wax, and dermatologic consultation were obtained in St. Paul at the expense of the individuals except in the case of three children whose care was paid for by the County Welfare Department. The cost of the professional services, special teacher, janitorial services, and medical and school supplies was about $2,400.

* From the Division of Dermatology, University of Minnesota, Dr. H. E. Michelson, Director.

EPIDEMIOLOGY

The exact origin of the local epidemic was not determined. It may be presumed that the disease entered from St. Paul, where the first case was noted in 1941, with additional cases recognized in 1942 and 1943 and epidemic spread in and after 1944. In June 1945, the first diagnosis in New Richmond was proved by Wood's light and mycologic culture, but later examination of the school population showed that the infection had been present for several months in other children. In order to establish, if possible, the source of the spread, a search was made for the earliest cases. Review of the records and histories brought out two boys, W. H. and W. D., whose families occupied the same house. Here the story becomes somewhat confused. In November 1944, W. D. was examined by his family physician, who made a clinical diagnosis of ringworm of the scalp. The mother insisted that her son had acquired the infection from W. H., who had moved to New Richmond from Balsam Lake, Wisconsin, where he had played at a summer resort with children from Chicago, Minneapolis and St. Paul. In this youngster, however, the diagnosis was not made until March 1945. W. D. had not been out of town and had always lived in New Richmond.

In an attempt to determine the manner of spread of infection, one of the authors questioned the mothers of about 15 infected children, including those suspected of having been among the first infected. All but one, a five-year-old, had attended the only theater in the community. This child had no siblings, but had patronized a barber shop. All but three had patronized one or the other of the community's two barber shops. Of these three who had not patronized a barber shop, one boy had two infected brothers, making it unwise to draw conclusions as to how he acquired the infection. The other two were girls with noninfected siblings; they had attended the theater, allowing at least a suspicion that their disease was acquired there. At the height of the epidemic the front rows of theater seats were examined by Wood's light without demonstrating infected hairs. On a single examination fluorescent hairs were not found in clippings from the two barber shops. In the Hagerstown study the authors listed the principal sources of contact as poor hygiene at home, play, exchanging of caps, the backs of theater seats, and in barber shops, concluding that only in the barber shops was there more exposure for the boys than for the girls, explaining the lower incidence in the latter. From the present study it would seem reasonable to conclude that both theater and barber shop are likely places for acquiring the disease. The importance of spread by close physical contacts is well illustrated by the fact that siblings were infected in more than half the cases (six families accounted for 14 cases while there were 12 examples of single infections in a household). Probably the more vigorous physical contacts of boys accounts for the sex distribution of infection, 22 boys and 4 girls.

Because of the small size of the epidemic it was surprising to note infection occurring at almost all ages from 1 month to 14 years, excepting 3, 6, and 13 years. The peak of frequency was noted at 7 and 8 years (5 and 4 cases respectively). In most of the reported epidemics the highest incidence was about this age. (In St. Paul the average age was 7.2 years; Carrick found the greatest number between 6 and 10 years; Schwartz reported that 58 per cent of the boys and 77 per cent of the girls were under 11 years.[4]) It is difficult to account for the high incidence at this age. Spontaneously curative endocrine factors are thought not to become effective until 10 or 12 years of age or even later. *In small communities the younger children* are less likely to patronize barber shops, but in this series they were found to be infected frequently. The high incidence at a lower age level might be explained by the fact that the shorter the child, the more likely is the head to be rubbed on the back of a theater seat.

TABLE 1

Number Infected at Various Ages

Age	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Number	1	0	0	1	2	0	5	4	3	1	3	1	0	1

RESULTS OF TREATMENT

The results of treatment were not reviewed in the case of six children, two of whom failed to consult physicians, two moved out of the community, and one was only one month of age.

Even if roentgen epilation be regarded as the best therapeutic aid, it is impractical to apply this form of treatment to all infected children in a community at some distance from qualified dermatologic and roentgenologic personnel and equipment. In this instance nine children were treated without this aid, selected partly by less extensive or less severe involvement. Seven of these patients (77 per cent) were cured within three months and the remainder by six months. Seventeen children had x-ray treatment applied. Seven (41 per cent) were cured within the first three months, and seven more in the second three months (a cumulative total of 82 per cent). Of the three remaining infected cases, two (12 per cent) were cured at 12 months and one was still infected, but improving, at

17 months. In this study both groups of patients (with and without roentgen epilation) received the same care by the same nurse. This consisted of simple local applications, such as ammoniated mercury ointment, and almost daily manual epilation in Wood's light. It seems fair to conclude that in the presence of infection of limited extent, manual epilation and daily topical application of fungicides can be expected to cure most or all of the infections within a reasonable period.

Grouping the cases treated with and without x-rays it is noted that 54 per cent were cured within three months, 88 per cent in six months, and after 12 months the infection was still present in only one instance (4 per cent). In the St. Paul series 46 per cent of 486 cases were cured within three months. Reviewing the results of treatment in a private office practice in St. Paul, it was noted that 34 patients received all their care without attendance at the civic treatment center (28 had epilation by x-ray and six did not). In this series 53 per cent were cured at three months and 82 per cent at six months, with infection persisting longer than 12 months in 1 case (3 per cent). From the viewpoint of therapeutic results for the individual it seems that the methods used in the New Richmond epidemic were successful as compared with results in civic control of a large epidemic or in private practice. From the viewpoint of control of the epidemic the described methods were successful in that no infected school children were found on thorough examination by Wood's light on re-opening of school the following year (September 1946).

COMMENT

Although there have not been published reports of epidemics of ringworm of the scalp in small American communities, there have been a few reports of scattered instances of infection and the Minnesota figures make it evident that small epidemics may be expected. (Of approximately 1,000 cases reported, almost 100 were observed in villages and in smaller cities.) Most small communities are unprepared to face the problem. Possible approaches are outlined by the New York Committee recommendations [5] and by the extensive reports on the epidemics in Hagerstown and St. Paul. Experience in New Richmond suggests the following procedures, after infection has been noted in the children of a small city. (1) Wood's light should be used for examination of the scalps of all school children under 15 years, whether in public, parochial, or other private schools. Still younger children should be brought in for examination if they are siblings or other close contacts of those found to be infected. (2) Infected children should be identified by clipping the hair and by the wearing of caps at all times. They can then be kept more easily from attending barber shops and theaters. (3) Isolation in special class rooms makes it easier to keep them from playing with other children, and facilitates treatment or supervision by a school or public health nurse. (4) After treatment a child should not be re-admitted to regular classes until several examinations have failed to demonstrate fluorescent hair, and after re-admission the child should be examined again in 30 days. (5) New students should not be allowed to begin classes until after examination in Wood's light. (6) The entire school population should be re-examined periodically until all cases have been cured. (7) All barbers in the community should be made familiar with the problem, advised not to work on cases where infection is suspected, and should be advised to follow the sterilization procedure for clippers as outlined by the United States Public Health Service. From the present study it is concluded that the transfer of infection is most likely to be from personal contacts in the home or at outside play, but theaters as well as barbor shops are possible sources of infection.

It is hard to set rigid rules for a program of treatment. If the cases are few they can be treated privately, but the school nurse must then have absolute authority regarding exclusion from or re-admission to school. When infected cases are more numerous the treatment should be publicly supported and controlled. It would be dangerous to insist upon roentgenologic epilation, even though this may result in a more rapid cure.

CONCLUSIONS

The small number of infected cases in this report on New Richmond might suggest a relative lack of importance of this epidemic, yet numerous other small communities will suffer comparable epidemics. Even if the larger cities are successful in eliminating epidemic ringworm of the scalp, the public health problem long will remain a large one if the disease once becomes widespread in smaller centers. This presentation shows that community co-operation rapidly can bring such epidemics to a close with relatively simple methods and at not too great an expense. In small communities the primary responsibility will have to be that of a competent school nurse who can be trained quickly in the use of Wood's light. Radiotherapy and dermatologic advice and supervision can usually be obtained without traveling too far or paying too much. The teachers and parents must thoroughly understand the problem. Most important of

all, the local physicians must decide that the problem is one of public health and, except for co-operation, that the local physician can offer little or no direct therapeutic contribution.

On the basis of experience in a minor epidemic of ringworm of the scalp in a small city, it is thought that such epidemics can be brought under control quite rapidly by application of the relatively simple procedures outlined in this presentation. Early recognition of infection will mean that the involvement is more restricted in extent and will probably respond to local applications and repeated manual epilation of infected hair after clipping the entire scalp. X-rays need be used only when simple treatment has failed or when the infection is fairly widespread when first recognized. After epilation by x-rays the child's further treatment can be carried on within the local community if the nurse has been properly trained.

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BOOK REVIEWS (Continued from Page 178)

succeeds admirably, although it may be questioned whether the great increase in the knowledge of medicine has not made it impossible to be as successful as were the editors of 20 and more years ago. It will probably be the choice by those who prefer the personal viewpoint of a single and distinguished author.

J. B. Y.

CARDIOVASCULAR DISEASES. By David Scherf, M.D., and Linn J. Boyd, M.D. 478 pages, 56 illustrations. Philadelphia, Lippincott, 1947. Price $10.00.

The authors' background for the writing of this book is that of long-standing interest in cardiology, numerous publications on the subject and experience in the field of teaching. As a result they have produced a practical volume on cardiovascular disease not written especially for the specialist in the heart diseases, but a book of worth to the average internist and general practitioner.

The reviewer is struck especially by the readability and clarity of the discussions of the pathologic physiology of such items as dyspnea, orthopnea, pulmonary edema and the like. This material is presented adequately but still with simplicity. Similarly, the presentation of the subjects of hypertrophy and dilatation of the several cardiac portions and the mechanism of compensation and decompensation are clearly set forth. Hemodynamics, venous thrombosis and embolism are well covered. There is a worthwhile consideration of reflex effect upon the cardiovascular system from such sources as the respiratory and digestive tracts.

The chapters given over to the clinical descriptions of the various types of valvular, myocardial and congenital heart disease, cover the usual items of etiology, symptomatology and physical findings. Good use is made of electrocardiograms and x-ray pictures in these sections. Discussion of treatment of the several forms of heart disease is included in their respective chapters. The diagnostic problems of anginal pain are considered in detail. Interesting sections are given over to the heart in endocrine disturbances as in thyroid disease and in the menopause. Chapters on aortic disease are included in the book.

The reviewer feels this is a valuable volume for the general practitioner who has not time to make extensive studies in the field yet wishes to have up-to-date knowledge at hand. As indicated above this book offers good coverage not only of the clinical aspects of heart disease, but also very readable discussions of fundamental physiology, normal and abnormal, so important in the understanding of cardiovascular abnormalities.

R. H. K.

MANAGING MEN. By S. H. Kraines, M.D. Published by the author, 30 N. Michigan, Chicago, Ill. 191 pages. $2.00.

This small volume, subtitled "Preventive Psychiatry," is avowedly written for the soldier, for the "unit leader both commissioned and non-commissioned." Its author, a clinical assistant professor of psychiatry at the University of Illinois, College of Medicine, served as a Major, Medical Corps, from

(Please turn to Page 188)

Ulcerative colitis always has been a disease intriguing from the etiologic and most difficult to manage from the therapeutic viewpoints. The author reviews the principles of treatment which need to be applied with exceeding patience.

Ulcerative Colitis*

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Many patients who say they have colitis do not. "Colitis" means, literally, inflammation of the colon and by the very nature of the process is serious. The term "ulcerative colitis" is an inclusive one, encompassing every ulcerative process affecting the lower bowel. Bargen [1] divides these into nine types, as follows:

Type I is thrombo-ulcerative colitis, formerly called idiopathic ulcerative colitis. The earliest and severest manifestations appear in the rectum and spread persistently and distressingly until the entire colon, and even the lower part of the ileum, is involved.

Type II differs from Type I in that the segments within reach of the sigmoidoscope are not involved by the pathologic process. The existence and the extent of the lesion are revealed by the roentgen examination. No common bacteriologic or other etiologic agent has been determined for this type.

Type III includes those in which the lesion is similar to that of Type II except that those segments within reach of the proctosigmoidoscope are involved either alone or with segments of the colon above this level. This and Type II are not to be distinguished from each other except by the distribution of the ulcerative process in the intestine. As in Type II the causation is not clear—there may be a variety of causes. So, Types II and III are in reality different diseases from Type I; different not only in sites of election but also in etiology. Patients with ulcerative colitis Types I and II have had it for relatively a short time. Some cases may be secondary to other disease in the body though the term "idiopathic" could very aptly be applied here.

The remaining six types, not germane to the present discussion, include those due to tuberculosis, Endameba histolytica, dietary insufficiency, venereal lymphogranuloma or to allergic factors; finally, there is a type which occurs as a late phase of bacillary dysentery.

The correct classification of chronic ulcerative colitis into one of these types is usually, though not always, easy. It is done by correlating the history, physical examination, etc., with the proctoscopic and roentgen-ray findings. In fact, the importance of the expert use of the proctosigmoidoscope cannot be overestimated. When characteristic proctoscopic findings are lacking, roentgen-ray investigation assumes primary importance.

Further discussion will, in large part, be confined to Type I, the thrombo-ulcerative colitis or streptococcal ulcerative colitis, which is the form most commonly seen in practice. The first reference to it in literature was by Wilks and Moxon [2] in 1875, but no real clinical study was reported until 1919 when Logan [3] reported 119 cases. He spoke of it as a "Fearful and grave entity." Its progression is in this sequence; attack of the bowel through the blood stream by a micro-organism or its toxin, resulting in tiny hemorrhagic infarcts; formation of minute abscesses and the appearance of the diseased tissue, from the mucosal side, as a granular, bleeding surface.

Although many hypotheses for the cause of the disease have been advanced, we accept a streptococcal origin—that the disease is caused by infection by a specific micro-organism or groups of organisms. Extensive investigation by Bargen, and others, has established a diplostreptococcus as at least one of the main instigators of the disease. This is the "diplostreptococcus of Bargen" around which a rather formidable storm of controversy arose but which has somewhat subsided.

No particular type or race of people is especially susceptible to the condition. Ages vary from 2 to 80 but usually the patients are in the second to fourth decades. Infection of the upper respiratory tract seems an important factor in initiating the disease or a recurrence thereof. This is an especially significant item to bear in mind—that a simple cold can cause a recrudescence of a quiescent ulcerative colitis.

Bargen [1] stresses four stages in the pathologic changes. They are:

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Given before the Post Graduate meeting of the American College of Physicians in Pittsburgh, September 1946.

1. Diffuse inflammatory reaction with hyperemia in the mucous membrane.

2. Edema of the mucosa involving the same area as that of the hyperemia. The mucous membrane appears thick, red and boggy and is very easily traumatized by the end of the proctoscope. In no other disease is this trauma so characteristic; we consider it almost pathognomonic in itself.

3. Small yellowish spots, miliary abscesses, appear scattered diffusely throughout the wall. These ultimately rupture through the thin mucosal bowel lining, leaving open ulcers. These are the true ulcers of thrombo-ulcerative colitis and give the bowel the typical, diffuse, granular, bleeding, moth-eaten appearance. Contraction of the wall of the bowel is a constant feature and a cardinal diagnostic point. It may vary from the slightest degree of contraction to a stricture through which it is impossible to pass an instrument larger than a cystoscope. Proctoscopy shows only a bleeding, ulcerated tube and the characteristic lesions which will appear in 95 per cent of cases. In 20 per cent the rectum and sigmoid only are involved. When ulcers are present the condition of the intervening mucosa is important. In Type V, that due to Endameba histolytica, the mucosa between the ulcers is perfectly normal; in thrombo-ulcerative colitis it is inflamed.

DIAGNOSIS

The patient with advanced disease presents a drawn and anxious facies, loss of weight, and is obviously anemic. The desire to be near the toilet is constant because the colon having lost its haustrations and become a narrow tube, "material rushes through it like a pipe." In less advanced stages the patient appears only mildly ill and offers as his chief complaint the one word "diarrhea." The number of diarrheic stools depends on the stage of the disease and may vary from but two to three loose movements during the day to 20 or 30 in the daytime and eight to ten or more at night. Straining, griping and tenesmus are present to a greater or lesser degree in all cases. Some of this is mechanical in origin, for the bowel narrows in a funnel shape as it approaches the rectum. The rectal discharges in severe cases may, as Bargen points out, resemble the expectoration of patients with pneumonia. They have been described as "intestinal sputum." They may be streaked with blood or contain huge clots.

Summarizing the diagnostic features, they are: the dysentery, the characteristic appearance in the advanced stages with its anxiety and helplessness, anemia of varying degree, often a septic type of fever and an elevated sedimentation rate. Added to these are the proctoscopic and the roentgen-ray findings. These last are, in brief, a general contraction of the intestinal wall, changes in mobility and flexibility as detected by roentgenoscopy under manual control, and complete loss of haustrations. Often there can be noted a feathery edge of the bowel outline that is characteristic.

PROGNOSIS

Although present treatment leaves much to be desired, a distinct advance has been made. It must be considered, much as is tuberculosis or rheumatoid arthritis, "a progressive, destructive inflammation of the large intestine, in which to stem the tide, many measures must be brought into play; and the patient as well as the physician must learn long suffering and patience." At the first consultation with the patient, he should be immediately viewed from the long range viewpoint; the physician must see himself as responsible for the patient for the next two or three or five or ten years.

The hematologic picture of chronic ulcerative colitis furnishes information as to the severity of the disease and the prognosis regarding the individual patient. Garvin and Bargen [4] compared the blood findings of 125 consecutive patients in all stages with the clinical status. They confirmed the conclusions of Hamilton and Harvey [5] that the hematologic pattern is an image of the focal process. In active, uncomplicated forms of the disease there exists a hypochromic anemia, a normal leukocyte count with a marked shift to the left of the neutrophilic leukocytes, a grossly altered filament-nonfilament count and an increased sedimentation rate.

The hypochromic anemia is the result of the loss of blood from the bowel, altered gastro-intestinal physiology, inadequate diet and the direct effect of the infection. The normal or nearly normal leukocyte count is only apparent. Further study of these elements reveals that there is an increase in the neutrophils to as high as 90 per cent, marked immaturity and an alteration in nonfilamented neutrophils to 70 per cent of the total. In crises the total number of leukocytes may drop to 2,500 cells per cu. mm. or less and the filamented cells may fall to zero. In this situation the values for hemoglobin and erythrocytes decrease precipitously. The accelerated sedimentation rate can only be explained on the basis of a severe toxemia.[4]

Prognostic significance, then, is attached to the blood picture. In spite of temporary remission of

symptoms, real therapeutic progress has not been attained until there is significant improvement hematologically. Treatment should not be relaxed until all the elements have been returned to normal. As a rule, considerable improvement will be manifest clinically before it is reflected in the blood picture. In certain situations, there is real difficulty distinguishing symptoms due to activity of the disease and those due to permanently altered structure of the bowel. Even though both conditions may co-exist, the blood picture will reflect the focal activity.

Some patients can be restored to health and usefulness; others may have to rearrange their mode of living for years, to fit in with restrictions imposed on them by the fact that they are afflicted. Children under 12 withstand it poorly; on the other hand, if the onset is at age 60, the percentage of recovery is very high. Relapses are common, the chief causes being upper respiratory infections, mental and psychic trauma and lighting up of distant foci.

Carcinomatous degeneration through the medium of polyps which undergo malignant change is occasionally seen but in most cases of carcinomatous degeneration a very virulent type of malignancy without apparent polypoid transition occurs. Carcinoma develops in about 3 per cent of all cases of the disease and in 6.3 per cent of children less than 15 years old, according to Bargen.[1] If there is a change of symptoms such as rapid loss of weight, more pain and cramps, increased bleeding and appearance of an abdominal mass, a digital examination of the rectum should be done without waiting for proctoscopic facilities, remembering that 50 per cent of all tumors of the colon are within reach of the index finger.

TREATMENT

In treatment, we speak not of cure but of control and to this end there are employed:

1. Rest and recreation, which require little comment. Just as many a patient with duodenal ulcer has been rendered symptom-free by a vacation, just so will many a patient with chronic ulcerative colitis experience tremendous benefit from that or some other form of recreation.

2. Dieting, which, in the ulcerative colitis patient, represents a most difficult problem. Often the diet on which he has been subsisting is too greatly restricted, so that the patient has lost strength. Very often, too, there is little appetite or a complete anorexia. The first problem, then, is to create an appetite, regardless of the type of food. If there is some appetite, a start can be made on a high calorie, low residue diet having as its base, lean meat (especially pork), rice, white bread, sugar, strained cereals, eggs, butter and cream. Proteins should be given in every possible form. Here there is really more rationale for the use of amino acids than in duodenal ulcer. Of course, the low residue diet is ideal and should be used exclusively if the patient will eat it. However, the time frequently comes when the problem is to get the patient to eat anything. In such a situation, qualitative restrictions are abandoned by us as we cater completely to the patient's appetite, if any, regardless of how bizarre it may seem. In fact, we have told our residents, that the "basic" diet is anything that the patient will eat, regardless of what it consists.

3. Vitamins in yeast, cod liver oil, fruit juices, etc., need only be mentioned, as do the tablet forms in which many of these come. Vitamin C should be given in doses of 200 to 300 mg. a day . Vitamin K in some such form at Klotogen is needed when the prothrombin time is disturbed and should be given, 6 to 9 capsules a day.

4. Serums and vaccines. Serum from immunized horses has been used in severe cases. It is given intramuscularly every four hours starting with 0.1 cc. and increasing until 3 cc. is given. A few years ago we used it rather extensively, but decided that the results did not merit the expense and inconvenience involved. Many vaccines have been used and for each a certain efficacy has been claimed. The autogenous vaccine has had the largest acceptance, however, and not without some merit. When it can be made from a pure culture obtained from the base of an ulcer via the anoscope or proctoscope, and the vaccine prepared therefrom contains 2,000 million diplostreptococcus per cubic centimeter, it will frequently be found to be an effective aid in therapy. It is given every three to five days for several months, starting with 0.1 cc. doses, continuing up to 1.5 cc. Attempts to prepare a vaccine from stool cultures are unsatisfactory.

5. Drugs. The most efficient are the sulfonamides. Of this group the most effective are among the newest and the oldest—neoprontosil and sulfathalidine. Even newer than the latter is sulfacarizole, used in the same doses as sulafthalidine, 3 Gm. a day. Sulfathalidine is absorbed sparingly from the intestinal tract, is rapidly excreted into the urine and in vitro has been found to have two to four times the bacteriostatic activity of succinyl or sulfathiazole; in addition, smaller doses are effective. Penicillin is of benefit in cases wherein the disease process is quite active and in which secondary fibrosis and structural changes have not taken place to any great extent. In a fulminating case in which perforation is impending, liberal use of penicillin has been vital. Our most

recent case illustrating this was that of a girl of 21 in whom the current attack had been active for but ten weeks. In spite of all chemotherapy, except penicillin, her progress was rapidly downward until a temperature of 105° was reached and it was felt that perforation was imminent. Elimination of food by mouth and the use of 200,000 units of penicillin every three hours, apparently brought about a reversal of the process and she recovered. Korostoff and King[6] report having used it freely and say that the rectal ulcerations disappeared within one week after completion of a course of the drug. Subjective symptoms and the character of the stool also improved. Garvin[7] reported similarly satisfactory results of its use with the 156th General Hospital in England. Although a dosage of but 20,000 units was used, improvement was marked, both subjectively and objectively, the mucosal improvement being observed by him personally. Not infrequently, the sulfonamides are poorly tolerated by the patient with ulcerative colitis and, like various iron preparations, do more harm than good. We have one such under our care now. We have attempted, since her release from the hospital to keep her on intermittent courses of sulfathalidine, but the periods in which she is taking the drug are preceded by protests against it and are marked by no decrease in the number of stools but instead by loss of weight and appetite and a not inconsiderable depression. She insists that she always feels, eats and sleeps better when not taking the sulfathalidine. Only one of our cases has been treated with streptomycin and no benefit was apparent. It should be emphasized that no chemotherapeutic agent can be expected to restore to normal the physiologic function of an intestine which has become contracted and deformed by disease of long standing. All the drug can be expected to do is control symptoms due to active infection.

To give rest from too frequent bowel movements th opiates have a definite role. The camphorated tincture of opium in teaspoonful doses is most frequently used. The deodorized tincture in 5 to 15 minim doses is also effective, as is codein in ½ grain tablets. Bismuth is worthless. Insofar as possible, the number of movements should be cut down, for more movements seem to beget more movements. We often urge patients to resist the urge to have bowel movements for just that reason. Furthermore, "Reducing the number of bowel movements moderately appears to render the absorbable or locally acting drugs more effective by preventing their too rapid elimination from the intestine." For "cramps" papaverine grain 1 and extract of belladonna, grain ¾, are used as needed.[8]

Transfusions are of great importance and help. Amounts of 150 to 200 cc. are better than fewer, larger amounts. Such small transfusions should be given four or six days apart and given freely—not as desperate last resort measures.

Irrigations and instillations are mentioned only to be strongly condemned. Remembering that the disease extends through all coats of the bowel, of what avail can a mere washing of the mucosa be?

Parenteral fluids: The fluid requirement for 24 hours to get an adequate urine output of 1,200 to 1,500 cc. is two to three liters. The salt requirement for 24 hours is 2 to 5 Gm. of sodium chloride a day. If the patient eats, he gets this. If he can't or won't eat it must be given parenterally as normal saline. In general, Bargen believes, not more than two liters over and above the loss of fluid is needed; more than this is excessive and results in edema.

SURGERY

The chief indications for surgical interference used to include intractability to other treatment, but not now. They do include polyposis, neoplasm, stricture, perianal fissures, perforations and abscesses. Except for these surgery should be used very sparingly. However, if and when a patient with thrombo-ulcerative colitis has surgical indications, ileostomy and subsequent colectomy are the procedures of choice. Ileostomy alone offers little. Very occasionally, after ideostomy, enough healing will result to permit closing the stoma, but this is rare. Even after ileostomy, medical management must be carried on. A woman of 35 under our care now, had an ileostomy eight years ago but still has frequent bloody bowel movements from the rectum, night and day, in addition to the discharge through the ileostomy. The process is in no degree abated, the sedimentation rate persistently remaining above 50 mm. in one hour and her hypochromic anemia is still present. The mere act of shunting the fecal stream from the colon did not cure the disease. Colostomy is not considered in surgical treatment because the disease may not stop at the site of the colostomy but ride right on over it. We have been impressed with the large number of patients with a colectomy on one of the larger surgical services we visited, since we view it as a rather heroic procedure. It brought up the question that Bargen and Whittaker[9] have asked, "What about the bodily economy of the patient without a colon?" They analyzed the mental reactions of 40 patients after colectomy and found that once habits are established, patients without a colon can live just as full and happy a life as anyone else. We encountered a similar reaction in

the ones we interviewed. No demonstrable deficiencies follow colectomy.

Considering the various forms of treatment of ulcerative colitis herein discussed—and others—some gastroenterologists feel that considerable has been accomplished in its care, others feel otherwise. One of those with the most extensive experience in the disease told me recently, "Frankly, I'm stumped. I feel that we have made no progress worth speaking of in the last 25 years." It would seem, however, that not enough stress has been laid on the importance of tenacity in treatment. In this regard we gastroenterologists might take a leaf from the experience of those treating rheumatism. They look forward to the time when the disease has burned itself out, just as ulcerative colitis may ultimately do. They are then prepared to work with what remains and, insofar as possible, re-establish function. Similarly we should work with the scarred and contracted colon that the acute process has left. It is often remarkable how efficient such a bowel can be; how nearly normal a life can be enjoyed by the patient.



FIGURE 1.

Figure 1 shows the colon of a girl of 16 when first seen in 1929. Her home was in a suburb of Pittsburgh but so frequent were her bowel movements that street car, bus or private automobile could not be used to bring her to our office; instead, trains with toilet facilities had to be used. From the Pittsburgh station to this office, a distance of seven blocks, the course had to be from one department store rest room to another. After months of vaccine therapy with a pure culture of the diplococcus of Bargen she was vastly improved and, whereas she had at first been a recluse, withdrawing from school, she later returned to school and finished second in her class. She was able to indulge in theatricals and gymnastics and, aided by a rectal stricture which we were careful to preserve, have but three or four bowel movements, or less, a day, and none at night. This very desirable and relatively satisfactory situation prevailed for two years until she eloped and married below her social stratum. The attendant furore had its expected effect—her diarrhea recurred with blood and pus, her weight loss amounted to 28 pounds. At the height of the flare-up she had an appendectomy performed in an adjoining state, followed by peritonitis. For many months her invalidism was extreme. In about a year, however, she was divorced and in a short time became convalescent; two years later she remarried under auspicious circumstances and is now the mother of two children, living a practically normal, healthy life. This she is doing with a grossly deformed colon and despite operative and psychic trauma of no small degree.



FIGURE 2.

Figure 2 shows the colon of a woman of 40 who has had ulcerative colitis since she was 28. Before coming under our care she experienced all the stigmata of the disease with diarrhea, blood and pus in her stools, loss of weight, anorexia, etc. When we first saw her the sulfonamides were just becoming available and on them most of her progress has been made. After a year or two of rather concentrated treatment, chiefly with sulfathiazole, she became quite comfortable and had as her chief complaint the inconvenience of the frequent bowel movements. For nearly three additional years we kept her on sulfathiazole, two weeks out of three. This was a very satisfactory regime and she was able to pursue a quite active social life, in

addition to her home duties. The only recurrences were on the occasion of an upper respiratory infection to which she always responded badly. In spite of a colon devoid of all haustration, the result of a long standing ulcerative colitis, and with many severe reactions to colds and other infections, she lives and enjoys a normal, active existence.

These two cases illustrate the reward that comes from not growing weary in the treatment of these unfortunates. Once their care is undertaken, the physician-in-charge must be resigned to the ordeal of facing the same patient, the same relatives, the same odor and the same plaint of dissatisfaction, not infrequently being told that a friend had colitis and was cured in a week with colonic irrigations!

SUMMARY

"A fearful and grave entity," ulcerative colitis is amenable to control but scarcely to cure. Opinions vary as to the value of the various therapies available. Vaccines, the sulfonamides and penicillin are all effective to some degree in most cases. But the most important feature is the advisability, the absolute necessity, of continuing treatment until the infection itself has subsided. Many an invalid will thus be restored to a useful life. Patience on the part of the physician must be limitless because, ultimately, unless the patient dies, the disease will, in all probability, like arthritis, burn itself out, leaving embers with which the patient must live and on which his medical advisor must build.

5001 Jenkins Arcade

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BOOK REVIEWS (Continued from Page 182)

1942 to 1946 and the book is an outgrowth of several years' experience as a psychiatrist in a Replacement Training Center.

Although not clearly indicated in the Table of Contents, which, by the way, contains a synopsis of the chapters, the book is divided into two sections. The first eleven chapters list the qualities necessary to the good soldier, present certain psychiatric principles and discuss such things as the pre-army development of the soldiers' personality; army environment as a cause of poor soldiers; teaching of "group sessions"; attitude in relation to the good and poor soldier with lectures (intended for soldiers) on army life and training; personal problems as a cause of poor soldiers, the personal problem questionnaire; physical difficulties in relation to soldiering, including the matter of malingering; morale factors and AWOL; and, attitudes toward war.

Section II discusses psychiatric problems among soldiers and the management of fear. The subjects include feeble mindedness, the neuroses, psychopathic personalities and the psychoses. Not only are these various conditions described and defined but the causes, physical signs and symptoms and recognition of them are presented.

Information is given on the training and management of the more simple conditions. In the section on fear, considerable detail is devoted to definitions and an explanation of its nature, to signs of fear, to preventive measures and the part played by discipline.

There are numerous illustrative case reports, particularly in Section II. The appendix contains a series of "Advisor Bulletins" on reasons for our entering into the war and for fighting, prepared originally for issue to the troops. Although there are only 194 pages, much of the material is in relatively small print so that the actual material is greater than appears.

The book is written in language for the lay person and is intended for the use of some, at least, who are without special training or even an advanced general education. It is not, however, unduly "written down" and although perhaps a bit difficult in places for the untrained, should, in general, prove understandable.

This book is intended for use in the army. Nevertheless, it contains much of interest and value to the physician in civilian life.

J. B. Y.

There is more to the management of a patient with heart disease than writing prescriptions for digitalis and diuretics.

The General Care of Cardiac Patients*

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CHICAGO, ILLINOIS

Because few diseases strike more terror to lay people than does heart disease and because heart disease, to the layman, connotes an almost certain death and very probably a sudden death, it behooves the physician to be sure of his diagnosis. Except for acute coronary accidents, cardiac death itself is rarely both sudden and unexpected. Most instances of organic heart disease progress relatively slowly, often with relatively few symptoms, and not infrequently, the patient dies of some cause unrelated to heart disease. Like generals, most cardiacs die in bed. There is ample warning over a very considerable period of time to the physician, family and often to the patient himself.

Many laymen, when told that they have heart trouble, live a life filled with fear and usually with a much restricted range of activity. Many functional conditions produce symptoms suggestive of heart impairment, when in reality, the heart is normal. More people think they have heart disease than have it. Several years ago, Christian wrote as follows:

> Many physicians frequently make the mistake of diagnosing heart disease when it does not exist, and making such a mistaken diagnosis, plan an incorrect form of treatment, which, in its execution, brings harm rather than benefit to the patient. The harm comes not from any influence of a deleterious nature on the cardiac mechanism, but by its limitations and incident fears, it brings totally unwarranted disturbances to the patient's habits of life, to his occupation, possibly causing entirely unnecessary economic losses, and, most important of all, to his nervous mechanism, resulting in worries and fears, which are far more disturbing than would be actual pain.

It is often a monumental task to disabuse the patient's mind and to dispel the fears engendered by such a mistaken diagnosis, or by a chance word or statement by the physician or his associates. Consequently, as far as is possible, the correct diagnosis—anatomic, etiologic and functional—is to be sought and proper treatment based on this diagnosis in order that the best results may be obtained. Sir Thomas Lewis stated, "It is with the symptoms of the disease that the patient and that the doctor mainly contend; and the symptoms of heart disease may be said to derive almost exclusively from faults in function. Therefore in managing our patients our thoughts must be set in terms of function and not of structure."

When confronted with a patient with symptoms which might be due to heart disease, we must proceed step by step, asking ourselves a series of questions:

First: Is heart disease the cause? There must follow careful consideration and evaluation of such symptoms as rapid weak or irregular pulse, air hunger, pallor, cyanosis, syncope, collapse, precordial distress or pain, very high or low blood pressure, etc. It must always be borne in mind that any one, even those with damaged hearts, may have any type of emergency such as gallbladder colic, ruptured peptic ulcer, peripheral vascular shock, internal hemorrhage with shock, pulmonary embolism, syncopes of cerebral origin, and the like. We must be ever watchful of the problem of functional systolic murmurs, the paradox of paroxysmal tachycardia in otherwise sound hearts, the excitement associated with an unstable pulse with extrasystoles, and the frightening symptoms of neurocirculatory asthenia. Here again let it be said that bad prognoses disable more people than do their hearts. In the absence of major presaging events, spontaneous heart disease is unlikely. There are a limited number of symptoms and signs of organic heart disease:

1. Definite cardiac enlargement. Heart disease may be present without cardiac enlargement, however.
2. Presence of a definite diastolic murmur or a diastolic gallop.
3. Certain constant, often intense, systolic murmurs, particularly if accompanied by a basal, systolic thrill.
4. Certain arrhythmias, notably auricular fibrillation or flutter; various types and grades of block; pulsus alternans.
5. Certain electrocardiographic changes.
6. Pericardial friction.

Only after a careful history, examination and observation can one state safely that heart disease is or is not present.

* From the Department of Medicine, Northwestern University Medical School, Chicago, Ill.

Second, we ask ourselves: Is there potential heart disease? Expressed differently, it may be said that we proceed with the examination and observation with the attitude that the heart is under indictment on circumstantial evidence, but is not yet convicted. There may be foreboding clinical signs such as obesity, previous serious febrile illnesses (notably rheumatic fever and chorea), thyrotoxicosis, myxedema, various deficiency states, degenerative diseases, and chronic emphysema which warn us to anticipate future developments. Obviously, in these circumstances, the primary condition is our first consideration and not the heart.

Third, we ask: Is there acute heart failure? Does threat of rapid heart failure exist? In this contingency there is imminent danger of death. In the management of these cases, the determination of the precise cause is, for the moment, subordinate to the immediate need of proper treatment. Emergency treatment is imperative whether the condition is the result of a coronary accident, pulmonary embolism, right heart dilatation, pulmonary edema, extreme paroxysmal ventricular tachycardia or sudden embarrassment of a previously damaged heart with advanced valvular lesions or chronic myocardial disease. Resort must be had to morphine, papaverine, atropine, adrenalin, caffein, intravenous xanthine derivatives, coramine and digitalis, as the use of these drugs is indicated. Also to the administration of oxygen, to venesection or application of tourniquets to the extremities, injection of concentrated glucose solutions for dehydration of the lungs and nourishment of the heart muscle.

Finally, we consider the question: Is there chronic heart failure? A heart damaged in any of its component parts from any cause, can ultimately drift into the class of chronic heart failure (congestive failure). The heart simply does not meet the patient's needs. In observing a patient with heart disease it is most important to bear in mind the factors that lead to heart failure. Inasmuch as the original causes, rheumatic fever, arteriosclerosis and hypertension, usually cannot be prevented, great care must be exercised in protecting the cardiac patient against aggravating or precipitating causes. These include such things as infection or factors which increase the work of the heart, excessive physical effort, intense emotional strain, obesity, pregnancy, anemia, hyperthyroidism, and any condition causing acceleration of the heart rate. Insofar as these can be prevented, just so far will ultimate heart failure be delayed. The full signs of congestive failure eventually appear. Irrespective of the original cause the end result is the same; as Baltzan has stated, "Chronic congestive heart failure is an entity despite the pedigree." Consequently management does not entail the burden of making special allowances in respect to the cause of the failure with the notable exceptions of constrictive pericarditis and pericarditis with effusion which may require additional physical measures for relief.

Even in serious forms of heart disease, one should recognize the fact that functional recovery may be so complete that the outlook is good for many years. Experience has shown that much can be accomplished by the natural processes of healing and sensible attention to the details of daily living. The general care of cardiac patients, aside from the use of certain drugs and specific measures for special conditions, should include: (1) optimism to bolster the patient's morale and to allay his fears; (2) restriction of activity, and rehabilitation; (3) measures to induce comfort and tolerance; (4) prevention of further damage to an already damaged heart.

The patient looks forward to the visit of his physician usually as the most important event of the day. He responds to encouragement and assurance that favorable progress is being made, particularly if the physician by his manner and well chosen statements inspires confidence. Repeated efforts to allay the patient's fears and anxiety state, however time consuming, are necessary and well worth while.

The problem is the same through all ages from childhood to senescence: *To teach and encourage the patient to lead as normal a life as is consistent with safety; to avoid undue strain on an imperfect or poorly functioning heart.* In early childhood and adolescence, more supervision is necessary than is the case in older persons. Children can be made to understand their condition, accept restriction of activity, and develop a real sense of responsibility to a surprising degree. The physician often has more difficulty in educating the parents to a complete understanding of the situation on an intellectual plane rather than on an emotional level, to obtain the most helpful kind of co-operation and care for the benefit of the patient. Threats may cause timidity, while too much sympathy may lead to self-pity. During adolescence the struggle between the tendency to over-activity on the one hand and timidity and self-pity on the other hand is often a difficult one. Constant guidance and encouragement are particularly necessary during this stage. Adolescence is too often a difficult period of life even when a child is endowed with perfect health. It is during this time that psychologic adjustments must be made because of restrictions of physical activities, decisions as to the preparation for life by education and training, development of hobbies or interests to-

wards some gainful occupation, or a career compatible with the limitations of physical activity necessarily imposed in each case. The earlier in life the most suitable adjustment is made the better.

In middle age adjustments are more easily made. Much difficulty is experienced, however, in convincing many such patients that one or more daily rest periods are desirable and that frequent short vacations or longer periods of relaxation from time to time are very advantageous. Many adults fail to realize the importance of avoiding prolonged physical or mental strain, although they are well aware of the danger of sudden, unusual effort. In the aged, the heart responds less well than in the young. It has been well said that age is the greatest injury we have to endure. Age imposes its own limitations; further restrictions and limitations because of heart disease often seem too great a burden for the patient to bear. He develops an attitude of helplessness as well as despair. What's the use of trying to carry on? Compromises must be made and concessions must be granted to obtain a delicate balance between optimum restrictions of activities and happiness and contentment on the part of the patient consistent with reasonable safety.

Recently there has been a revision of the principle that absolute bed rest is essential in the management of cardiac failure. The object was to rest the heart. However, many patients are breathless under this regime and either sit up or walk about to obtain relief. Some actually regress when forced to remain in bed. There is a shift of fluid to the back and lungs—often hydrothorax develops—the vital capacity is decreased. Edema of the lower extremities is less incapacitating though unsightly. As someone has said "patients do not breathe with their legs." Peters showed on clinical investigation that "when the recumbent position is assumed, fluid leaves tissue spaces, enters the circulation, the blood volume increases, the blood becomes more dilute and the venous pressure increases." When this occurs more rather than less work is required of the heart. The purpose to rest the affected part has been defeated. Not infrequently there may arise such untoward complications and sequelae as an acute urinary retention from an enlarged prostate previously not disturbing, thrombophlebitis of the legs with or without pulmonary embolism, hypostasis in the lungs with congestion, and trophic disturbances of the integument. Last year in an address before the Institute of Medicine in Chicago, Levine said, "In many cases of congestive failure, especially where breathlessness is the major threat, rest in bed is harmful. A back rest or even an adjustable hospital bed does not do away entirely with these ill effects. Such patients are treated more successfully if kept in a chair during the day and if the head of the bed in which they sleep at night is lifted about nine inches by the use of shock blocks under the head of the bed." I must not neglect the opportunity at this point to mention the use and abuse of the bed pan, often regarded as an instrument of torture and accursed by males in particular. Men make poor "Pan Americans." In my experience, the use of a commode is less trying, less of an effort and far more satisfying in most instances. Bathroom privileges are granted as soon as it is safe to do so.

As compensation is regained the patient may have massage with passive movements, resistance and breathing exercises, followed by graduated exercise in the open air and sunlight and a return to his useful and gainful occupation as early as is expedient.

We have altered our former attitude towards a restricted intake of salt and water and fluids. Now that it has become established that if the sodium ion is restricted markedly, fluids can be given much more freely, the thirsty, dehydrated cardiacs with parched tongues and begging for water need not be seen any more. The sodium must be reduced in the food by the use of a low-sodium diet. Sodium in the form of the bicarbonate or phosphate or other preparations containing sodium should also be prohibited.

A word about spas. The chief benefit of a sojourn at the spa for a number of weeks occurs when a daily program is outlined in detail by a medical advisor—a carefully prescribed diet, advice as to the type and frequency of the baths and massage, the amount of physical activity, indicated periods of mental and physical relaxation and recreation. Such sojourns are often an excellent opportunity to teach a patient how best to live with his ailment. Spas are too costly for the average patient. Some physicians contend that most of the benefits claimed are psychologic.

If properly supervised, occupational therapy is often quite beneficial. Its chief objects are to arouse interest, courage and confidence; to exercise mind and body in healthy activity; to overcome functional disability and to re-establish a capacity for industrial and social usefulness.

Of great value in the treatment of heart failure has been the discovery and the use of the mercurial diuretics. They are more effective after a preliminary course of ammonium chloride, particularly if there is peripheral edema or anasarca. They are not used often enough in patients with cardiac dyspnea, or nocturnal dyspnea without evidence of peripheral edema or pulmonary engorgement. Under such circumstances they may furnish dramatic relief. Mercurial

diuretics may be repeated over long periods of time. It is well to remember that small doses (0.5 to 1.0 cc.) are often as effective and occasionally more effective than doses of 2 cc. or more. In the aged or those beyond middle age it is a good precaution to examine the prostate for hypertrophy before administering a mercurial diuretic because of the real danger of acute urinary retention with dilatation of, and damage to, the urinary bladder, if potential obstruction is present.

The advent of the sulfonamides and the antibiotics has proved to be of great benefit in the treatment and prevention of heart disease. Bacterial endocarditis can now be cured in the majority of cases, especially if treatment is started early and persisted in for an adequate length of time. Endocarditis may be prevented in patients with already damaged hearts (either congenital or acquired) by the administration of these preparations during acute infections, particularly of the upper respiratory tract, and before and following the extraction of infected teeth or the removal of diseased tonsils.

Infections are always a potential if not an actual menace to the cardiac patient. While infections cannot always be prevented, their occurrence may be minimized with careful hygiene of the mouth and throat, together with all reasonable precautions to be taken in avoiding crowds, public gatherings, visits with or from persons with obvious acute respiratory infections and abstinence from promiscuous sexual contacts.

Finally, for the cardiac who has regained his compensation, who has made the requisite adjustments and settled down to living with his heart condition in the best possible manner, the physician can give some general advice as to healthy habits of living, to wit:

Live quietly and moderately.

Avoid all forms of excess.

Avoid severe outburst of passion or severe emotional states.

Develop a routine of work, rest periods and relaxation.

Eat simple wholesome food at regular meal times.

Be temperate in the use of alcoholic drinks. In older persons moderate amounts may be beneficial.

Tobacco should be used sparingly if at all, chiefly because of irritation of the respiratory passages which is conducive to cough and infection and may lead to severe heart strain.

Get long regular hours of sleep.

Take frequent vacations.

Have regular periodic check up by a physician in order that early signs of failure may be detected promptly and prompt treatment instituted. This will often save long periods of illness and much economic loss.

WHAT'S YOUR DIAGNOSIS?

A 38-year-old white carpenter was admitted to the Medical Service for the fourth time (in a period of 18 months) and died ten days later.

On the first admission (18 months before his death) the patient stated that he had been in good health until six months previously, when, shortly after a piece of timber fell on his left big toe, he developed deep aching pain in the region of his right hip and the joint became stiff and painful on motion. The pain and stiffness persisted for several months. He then developed a succession of vague aching pains in his upper extremities, apparently without swelling or tenderness of the joints. He described the appearance of lumps under the skin over the elbows, wrists and dorsum of the hands, which were nontender. The lumps would come and go, each lasting two to three weeks. Small tender lumps transiently appeared on his tongue, roof of mouth, ears and nose. Throughout the period of his illness he was intermittently aware of periods of chilliness, feverishness and night sweats. There was a persistent slightly productive cough. He lost 50 lb. in weight.

The essential findings on physical examination were evidence of weight loss, general glandular enlargement, several nontender, nonfixed subcutaneous nodules over elbows and left thigh, and inconstant mild asthmatic wheezes throughout both lung fields. The heart was normal and the liver and spleen not palpable. The ankles were slightly swollen and tender. There was an ill-defined pigmentation of the skin over the upper back. There was an anemia as represented by an average RBC count of 3.6 million. Leukocyte count and differential were normal with 1 to 4 per cent eosinophilia. Urine examinations revealed no abnormality. Sedimentation rate 36 mm./hr. Bru-

Case protocol given third- and fourth-year students for the clinicopathologic conference, Vanderbilt University School of Medicine, Nashville, Tenn.

cella agglutinations were negative and two blood cultures showed no growth. A chest plate showed marked hilar thickening and general increase in bronchovascular shadow. The electrocardiogram was normal. The patient was in the hospital three weeks. There was a low-grade swinging fever of 99° to 100° which gradually increased to a peak of 102° then subsided to the former level. During this time numerous pea-size to walnut-size subcutaneous nodules were observed to appear and disappear, mostly over various aspects of the extremities. The nodules were accompanied by a local burning sensation but were usually nontender, lasted about a week and left no obvious residua. On one occasion there was a generalized erythematous papular rash which cleared in a few days. He complained intermittently of muscle pains and pains about the joints which were considerably relieved by salicylates. He began to feel better and was discharged.

Two months later he developed chills, high fever, severe diarrhea and was admitted for the second time and found to have bacillary dysentery (Hiss-Russell organism cultured from stool). He was treated with sulfathiazole for a period of four days with apparent cure of his dysentery. The patient was not seen again for eight months. During this time he continued to complain of muscle pains and pains about his joints. There was feverishness from time to time and gradual increase of general weakness. Frequency of urination and nocturia became rather pronounced but without pain, burning or hematuria. There were vague, fleeting abdominal pains. Following a period of exertion he developed a sudden episode of substernal pain which was relieved when an ampule was broken under his nose. Following this there was mild orthopnea. He continued to notice recurrent crops of subcutaneous nodules. He was admitted to the hospital for the third time for further study. There were no further findings on physical examination or through laboratory studies except early clubbing of the fingers was noted and there were a few moist râles at both lung bases. The heart did not appear enlarged and there were no murmurs. No solid abdominal viscera were palpable. A chest plate showed no further changes and an electrocardiogram was normal. There was a low-grade afternoon fever of 100°.

He was admitted for the last time, two years after the onset of his illness. All of his complaints had persisted and in addition there appeared increasing exertional dyspnea, orthopnea and tachycardia. He described intermittent swelling of his abdomen and intermittent painful swelling of his eye lids. He also complained of insomnia, headaches, loss of memory, thickness of speech, and periods of confusion. During the month before admission he was confined to bed because of severe weakness and dyspnea. In the last few months there had been no chills and apparently very little fever. The subcutaneous nodules appeared in crops every two to three months lasting about a week. On this occasion he was seen to be severely chronically ill with pallor and yellowish tint to skin. Facies appeared acromegalic. The fingers were clubbed. Several subcutaneous nodules, as previously described, were present. The ocular fundi were not remarkable. There were a few scattered moist râles at the lung bases. The heart size could not be determined. The sounds were distant and of poor quality. No murmurs were heard. Rhythm was regular. B.P. 110/65. There were signs of fluid in the abdomen. The liver and spleen were not felt. There was pitting edema of the legs, back and abdominal wall. Large external hemorrhoids were present.

The course in the hospital was progressively downhill. A low-grade fever of 99° to 100° on admission subsided to normal. There was a tachycardia of 90 to 110. Dyspnea and orthopnea increased and he was placed in an oxygen tent and digitalized. Because of a severe anemia he was cautiously given a transfusion of 500 cc. of whole blood. He became progressively worse and developed Cheyne-Stokes respiration, a gallop rhythm and became irrational. He died quietly on the tenth hospital day.

LABORATORY DATA

(Last Admission)

Blood:
Erythrocyte Count: 1.4 to 2.1 million.
Hemoglobin: 6.5 Gm.
Leukocyte Count: 6,500.
Differential: Stabs 12%, Segs 52%, Lym 30%, Mono 3%, Bas 3%.
Stabs 7%, Segs 55%, Lym 32%, Mono 1%, Bas 1%, Eos 4%.
Serum N.P.N.: 29.
Serum Proteins: Alb. 3.0, Glob. 3.4, total 6.4.
Cholesterol: 84.
Urine: Sp. gr. 1.017, Alb. 0, Sugar 0; rare WBC, no RBC or casts.
Sp. gr. 1.023, Alb. 0, Sugar 0; 2–3 WBC, occasional casts.
Stool: No occult blood.
BMR: — 9%.
Venous Pressure: 250 mm. saline.
B.S.P.: Less than 2% retention in 30 minutes.
Chest Plate: Cardiac shadow is enlarged. Small amount of fluid in left base. Thickened pleura at right base. Fibrosis in the uppers. Passive congestion both lowers.
Electrocardiogram: Rate 93, P-R 0.16, QRS 0.08; QRS 1, 2, 3 low; R_4 absent; T_1 and T_2 low, T_3 flat, T_4 inverted.

(For diagnosis, see page 214)

Management of the Nephrotic Syndrome*

GEORGE E. FARRAR, JR., M.D., CHARLES F. SACKETT, M.D., AND JOAN H. LONG, M.D.

The nephrotic syndrome presents a difficult and trying therapeutic problem. Specific treatment is not possible until the etiology is more thoroughly understood. In general, the nephrotic syndrome is the clinical manifestation of protein deficiency with hypoproteinemia, edema (without evidence of congestive heart failure), impaired absorption and utilization of protein, and often a loss of protein as albuminuria. There are numerous causative factors. The syndrome is seen in glomerulonephritis (see case abstract), malnutrition, arsenic poisoning, burns, amyloid disease, and the intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease) phase of diabetes mellitus. The edema has usually been considered to be due to a lowered blood osmotic pressure due to the loss of albumin in the urine, but an increased capillary permeability is probably a more fundamental abnormality. Chronic infections may play a role in this syndrome although an acute infection during the nephrotic stage may bring about a remission.

Treatment has followed several lines: An attempt to increase the colloid osmotic pressure of the blood by the intravenous administration of amino acids, human albumin, plasma, globin, or acacia, as well as by increasing the protein in the diet; an attempt to bring about diuresis by using an acid or neutral ash, low-sodium diet, and the administration of diuretics; and an eradication of foci of infection by drainage and the use of suitable chemotherapeutic or antibiotic agents.

CASE REPORT: A 59-year-old man, L. P., was admitted to Temple University Hospital on July 20, 1943 with the nephrotic stage of chronic glomerulonephritis. He had been perfectly well until the year before when he noticed ankle edema. This increased until at the time of admission he had pitting edema of the legs and thighs and edema of the eyelids. He had had frequent respiratory infections. Physical examination showed an alert, pale, middle-aged man, not uncomfortable, with generalized edema. Temperature, pulse and respiration were normal. The blood pressure was 190/110. Eyegrounds showed no retinitis and a grade 1 arteriosclerosis. There was no cardiac enlargement. Hemoglobin was 8 Gm., erythrocytes were 2.8 million. Total serum protein was 3.3 Gm. with an A/G ratio of 1.5. The urine showed a coagulum of albumin, a specific gravity ranging from 1.008 to 1.017 and an Addis count of 5 million erythrocytes, 4 million casts, and 1,000 mg. of protein. Blood urea nitrogen was 38 mg. per cent. Sedimentation rate was 28 mm. in 1 hour. X-rays showed apical infection of the lower left first molar and hypertrophic sinusitis, especially of the right maxillary antrum. The BMR was minus 14.

The patient was put on a salt-poor diet containing 100 Gm. of protein, 150 Gm. of carbohydrate, and 110 Gm. of fat. After two weeks of potassium nitrate, 2 Gm. four times a day, he was changed to enteric coated ammonium chloride tablets, 1 Gm. four times a day. He also received thyroid, 60 mg. twice a day. Intravenous therapy consisted of four 500 cc. transfusions of whole blood, 5,500 cc. of plasma, and three 500 cc. infusions of 6 per cent acacia, the latter being accompanied by 2 cc. of Mercupurin. The last infusion of acacia had to be discontinued because the patient developed cough and dyspnea during its administration. The best results as far as diuresis was concerned were obtained with the acacia plus the Mercupurin (see Fig. 1), but actually none of the measures brought about too marked an improvement. To clear up the foci of infection the tooth was extracted and the sinusitis was treated with ephedrine nose drops.

The patient developed ascites. On October 20 a paracentesis was performed and 7,000 cc. of milky fluid were withdrawn. On October 25 he developed fever and pain in the right side, found to be due to streptococcic empyema and peritonitis. These conditions were treated with intravenous sulfadiazine, fluids, and Wangensteen suction. At one point he was moribund but recovered and was discharged on November 12.

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Presented at The Eleventh Annual Postgraduate Institute, Philadelphia County Medical Society.

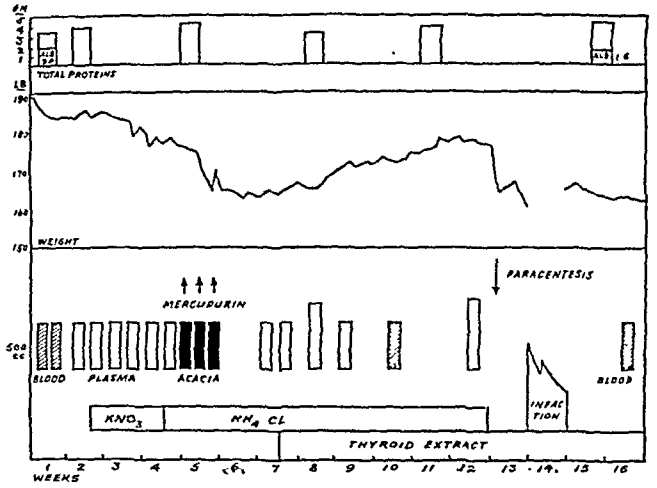


FIG. 1. The therapeutic measures employed and the course of patient L. P. during 16 weeks in the hospital. The total serum protein level in Gm. per 100 cc. is shown at the top of the chart and immediately below this is charted the body weight in pounds. Transfusions of whole blood are indicated by the blocks containing diagonal lines. Plasma infusions are shown as open blocks. The solid blocks indicate injections of acacia solution. The periods during which potassium nitrate, ammonium chloride and thyroid were administered are shown at the bottom. The episode of streptococcal empyema and peritonitis is also indicated.

The patient's discharge weight was 163 lb. in contrast to 188 lb. on admission. His total proteins were 4.3 with an A/G ratio of 0.59. He was still edematous.

At home he remained on a high-protein, low-salt diet and ammonium chloride and soon lost his edema. In the next six months he began to regain his edema but he did remarkably well for the next three years. He had a constantly elevated blood urea nitrogen (about 50 mg.) and his hemoglobin showed a tendency to drop. This was treated by transfusions of whole blood from time to time. During the latter part of 1946 he began to go "downhill," developed uremia, and died.

COMMENT

The aims of treatment are, first, to relieve the edema and, second, to correct the protein deficiency. Such aims are accomplished by means of diet, diuretics, and, if possible, by the correction of any etiologic factors.

Diet. An acid-ash, high-protein, low-sodium diet is a simple and satisfactory diet to use for the nephrotic syndrome.[1] Initially there should be six small feedings daily, each feeding consisting of one cup of milk *and* one egg *or* two slices of bread *or* one cup of cereal with butter, sugar, spices, and flavoring as desired. This supplies about 60 Gm. of protein daily. A low-sodium milk powder is available (Lonalac-Mead-Johnson). When the patient is able to eat a full diet, the next and final diet should consist of three to six meals daily providing at least two or three eggs, a quarter or a half pound of meat, fish, or fowl, and six slices of bread or servings of cereal. These meals should also provide not more than two cups of milk, one cup of vegetables, and one cup of fruits. The following may be eaten as desired: sugar, butter, gelatin (Jello), prunes, plums, and cranberries. Coffee and tea may be taken if not otherwise contraindicated. This diet provides 90 to 130 Gm. of protein daily. Food and foodstuffs to be avoided are: salt, soda, salted butter or bread or meat, cheese (except cottage), lima beans, spinach, dates, and raisins. This diet is summarized below.

ACID-ASH, HIGH-PROTEIN, LOW-SODIUM DIET

INITIAL

(Protein about 60 Gm.)

Six small feedings, each consisting of:
1 cup of milk *and* 1 egg
or
2 slices of bread
or
1 cup of cereal with butter, sugar, spices, and flavoring as desired

FINAL

(protein 90 to 130 Gm.)

Three to six meals to provide daily:

At least	*Not more than*
2 or 3 eggs	2 cups milk
¼ or ½ lb. meat, fish, or fowl	1 cup vegetables
6 slices bread or servings cereal	1 cup fruits

Avoid

Salt	Cheese (except cottage)
Soda	Lima beans
Salted butter or bread or meat, etc.	Spinach
Dates	Raisins

Ad lib.

Sugar	Prunes
Butter	Plums
Gelatin (Jello)	Cranberries

Coffee and tea if permissible

Fluids

1,500 cc. or more daily by mouth

Fluids. Daily 1,500 cc. or more should be taken by mouth along with the acid-ash diet.

Amino Acids. Since it is desirable that the daily protein consumption be 2 or even 3 Gm. of protein per kilogram (2.2 lb.) of body weight, it is often necessary to augment the dietary protein intake by means

of amino acids. This may be accomplished by 50 to 100 Gm. of a protein hydrolysate (equivalent to 75 per cent protein) orally or intravenously daily.[2] For intravenous injection a 5 per cent solution in 5 per cent dextrose in distilled water is given at a rate of 5 to 20 Gm. of amino acids per hour. *In nephrotic crises* amino acids intravenously daily are important in addition to penicillin and/or sulfadiazine.[3, 4]

Protein Diuretics. *Salt-poor Normal Human Serum Albumin.* This is a salt-poor substance that has the same viscosity as whole blood but is osmotically more active. Five grams in 20 cc. of diluent contain only about 0.15 Gm. of sodium chloride and these 20 cc. are equivalent to approximately 100 cc. of plasma. The dose is 25 Gm. (100 cc.) twice daily intravenously given very slowly. A single daily dose of 50 Gm. in 300 cc. or more of 10 per cent dextrose in distilled water intravenously may be given at a rate of 10 to 20 Gm. per hour. Albumin must be given for three to four weeks. In active or incipient congestive heart failure this material must be used very cautiously. Although salt-poor normal human serum albumin parenterally provides the largest amount of protein, it has two important drawbacks—it is not readily available and it is expensive.[2, 5, 6] Unfortunately, a considerable portion is lost in the urine.

Normal Human Plasma. This protein material is less effective (see Fig. 1) than the above because it provides less albumin and contains at least 5 Gm. of sodium chloride per liter. The dose is 750 cc. (requiring 1,500 cc. whole blood) to 1,000 cc. daily intravenously.

Globin, modified from human erythrocytes, is used in the same way as albumin and with similar results.

Other Diuretics. *Urea.* This may be given in 15-Gm. doses two to four times daily in fruit juice for one to three weeks. It is contraindicated when azotemia is present and during its use weekly determinations of the blood urea nitrogen should be made.[2]

Potassium Nitrate, Potassium Chloride, Ammonium Chloride, or Ammonium Nitrate. Any one of these drugs may be used in 3-Gm. doses three times daily after meals as half-gram enteric coated tablets for three days or longer at a time. With potassium salts the patient should be watched for arrhythmia and with ammonium salts for acidosis.

Dried Thyroid. This is to be used in 0.06-Gm. doses daily and may be increased by 0.06 Gm. daily at weekly intervals until diuresis or toxic manifestations occur.

Acacia. After diet and diuretics have failed to relieve edema, 500 cc. of 6 per cent acacia and 0.06 per cent sodium chloride in distilled water may be given intravenously slowly on alternate days for three (at the most, six) doses and 2 cc. of mercurophylline injection (U.S.P.) intravenously on alternate days.

Gelatin or Pectin. These have been used in the same way as acacia.

Other Measures. With the recent emphasis on the role of abnormal capillary permeability in the nephrotic syndrome, it has been suggested that rutin may be beneficial.[7] Calcium salts parenterally decrease this abnormal permeability but nitrogen retention may develop.

SUMMARY

1. Until more is understood about the nephrotic syndrome, specific therapy is not possible. Both hypoproteinemia and increased capillary permeability are concerned.

2. The aims of treatment are to relieve the edema and to correct the protein deficiency.

3. An acid-ash, high-protein, low-sodium diet, is the diet of choice, plus 1,500 cc. or more of fluids daily.

4. Salt-poor normal human serum albumin, plasma, urea, acacia, acid forming salts, potassium salts, and dried thyroid may also be employed.

5. In nephrotic crises amino acid preparations intravenously, plus penicillin and/or sulfadiazine, are indicated.

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Multiple sclerosis generally is accepted as a progressive disease of gloomy prognosis. The author presents a viewpoint contrary to this.

The Early Manifestations of Multiple Sclerosis*

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Multiple sclerosis is a degenerative disease of the nervous system and neither its cause nor cure is universally agreed upon. The essential pathologic features are scattered foci of demyelination in which the axis cylinders are relatively preserved and the astroglia have proliferated. Since the demyelinated and sclerotic foci are disseminated throughout the central nervous system and the cerebrospinal nerve roots, many neurologists prefer the term disseminated sclerosis while others, because of the focal inflammatory reaction in some cases, prefer the designation of disseminated encephalomyelitis. One characteristic clinical feature of multiple sclerosis is the development of more than one attack of neurologic dysfunction. This clinical feature is paralleled by the histopathologic finding of foci in various stages of disintegration indicative of different ages or dates of onset. Until a specific diagnostic test is developed, however, it will be very difficult to consider a single attack of neurologic dysfunction as being a manifestation of multiple sclerosis although in many instances such a diagnosis is made. Since Charcot's first accurate delineation of the disease in 1836 with his formulation of the famous triad—nystagmus, scanning speech and intention tremor—an increasingly large number of cases have been uncovered. At one time the disease was believed to be rare in the United States, but this has proved to be erroneous. Many deny that the disorder ever occurs in the full-blooded American Negro, but in the United States it is more difficult to be certain that a patient is of pure Negro inheritance than to establish the diagnosis of the disease entity under consideration.

DIAGNOSIS

The evolution of our diagnostic criteria for multiple sclerosis is paralleled by that of pulmonary tuberculosis. At one time the terms "consumption" and "white plague" were used to designate the latter disease because of the repeated hemorrhages, anemia, loss of weight and cachexia. With the discovery of the tubercle bacillus a laboratory test became available to facilitate the "early" diagnosis of that disorder. Today we realize that roentgenographic findings with both negative clinical and laboratory tests permit one to make an early diagnosis.

The demonstration of cases of advanced pulmonary tuberculosis in medical clinics interested in the early diagnosis of that disorder is no longer made, but neurologists are still prone to demonstrate cases of advanced multiple sclerosis as classical examples. As a result many physicians are so ingrained with the diagnostic criteria of multiple sclerosis as exemplified by the Charcot triad that they develop the "all or none" philosophy, refusing to consider such a diagnosis if one of the classical symptoms is lacking. Many advanced and even terminal forms of the disease, however, fail to show all of the classical symptoms.

How, then, can the early diagnosis of multiple sclerosis be made? I have found the following criteria of considerable value, being fully cognizant that in the absence of any specific test the diagnosis cannot be verified during life:

Age. Multiple sclerosis is a disease which generally makes its first appearance in adolescence or early adult life. Proved instances have rarely been observed in infants and young children and a first attack rarely occurs past 40 years of age. Just as with idiopathic epilepsy, however, an initial attack in the teens, twenties or thirties may be ignored or misdiagnosed and a train of severe neurologic symptoms in the late forties or fifties is looked upon as indicative of some other disorder.

Symptomatology. The early symptoms are generally an attack of double vision, an attack of poor vision, an attack of numbness in one or more extremities, an attack of unsteadiness in gait, a period characterized by urinary urgency without local disease or a period of extreme muscular fatigue. Less common presenting symptoms are sudden onset of sexual impotence without apparent cause, neuralgic pain particularly in the trigeminal region, aphasia and dysarthria, and even epileptiform convulsions and mental confusion.

DIPLOPIA. Double vision of momentary duration is not significant and is rarely a manifestation of multi-

* Presented at the Annual Session of the American College of Physicians, April 30, 1947, Chicago, Illinois.

ple sclerosis. The causes of diplopia are many and a careful study to eliminate meningovascular syphilis, polioencephalitis, myasthenia gravis, retro-orbital tumors, aneurysms of the circle of Willis, etc., must be made before multiple sclerosis is considered as the cause. The diplopia generally lasts weeks or months and frequently disappears completely. Wearing a shield over the affected eye generally suffices to relieve the inconvenience of the double vision.

Poor Vision. The sudden onset of blindness in one eye or the sensation of having a film over one eye is another common symptom. The acuity is diminished and the visual fields often show circumscribed defects or scotomas.

Numbness. The subjective feeling of numbness may involve any part of the body, but the extremities are most frequently affected. The right upper extremity, for example, may feel "dead" or "asleep" and if the individual forgets that he is holding something in his hand it may fall to the ground. Many times the patient complains of difficulty in placing his hand into his trouser pocket because of his poor position sense, or in identifying what he has grasped in his pocket without taking it out and looking at it.

Unsteadiness. Difficulty in walking is a common presenting symptom and the patient may be unaware of this fact until his friends accuse him of being intoxicated. The symptom is one of ataxia or dyssynergy with inability to walk heel to toe on a straight line, difficulty in standing in the Romberg position and loss of balance on turning about hurriedly. Unsteadiness in the upper extremities results in difficulty in bringing a full glass of water to the mouth or in the use of a fork or spoon.

Urinary Urgency. A classical symptom of multiple sclerosis is urinary urgency. When the patient becomes aware of the desire to urinate he has great difficulty in holding his urine and as a result he frequently soils his clothing. Inability to urinate after getting to the urinal and complete retention of the urine are other urologic complaints.

Fatigue. An acute attack of multiple sclerosis is often accompanied by severe asthenia, the patient feeling exhausted after a good night's rest. Many times this is interpreted as a psychoneurotic symptom or as a sign of myasthenia gravis. Rapid development of fatigue after doing a little work or walking a short distance are other manifestations.

Other Symptoms. Since the foci of demyelination may occur anywhere in the central nervous system, any type of symptom may occur. I have seen attacks of aphasia, dysarthria, mental confusion and epilepsy in known multiple sclerotics with no evidence of other disorders to account for the neurologic disturbance.

Clinical Course. The words remission and exacerbation are often used to describe the clinical course of multiple sclerosis. The symptoms resulting from a focus of disease may come on suddenly or may gradually increase in severity. The degree of remission is dependent upon the fate of the disease focus in the nervous system. If the initial stage of swelling of the myelin subsides with a complete or almost complete restitution to the norm, a complete disappearance of the symptoms follows. If, on the other hand, the disease goes on to demyelination, the symptomatology will persist for a longer period. Since in the diseased foci the myelin sheath loss is always of much greater intensity than the axis cylinder defect, it is apparent that axis cylinders persist despite their focal loss of myelin and it is probable that these axis cylinders may become functionally active again when the edema subsides and the products of degeneration are carried away. There is also a possibility that focal myelin regeneration plays a role in the remission. With degeneration of the axis cylinders and overgrowth of glia, however, the defect becomes permanent both clinically and anatomically. Thus, a symptom may remit partially with a certain amount of permanent defect or it may remit completely.

The exacerbation is not necessarily an exacerbation of the old diseased focus but rather an exacerbation of the disease with the development of new foci. Whereas one focus may clear up completely, a second focus may leave a 30 per cent defect, a third focus a 10 per cent defect, a fourth focus an 80 per cent defect. It is the summation of all of these permanent defects that leads to the symptomatology of the chronic form of multiple sclerosis. No form of treatment can result in a remission of the symptoms resulting from permanent loss of nerve fibers nor can the patient hope to enjoy a spontaneous remission.

The time interval between successive attacks may vary considerably, for as many as 20 years have elapsed in some cases between an initial attack of partial blindness attributed to retrobulbar neuritis and a subsequent attack of unsteadiness in gait. In more severe forms of the disorder the attacks may occur at monthly intervals or a second one may begin before an initial one subsides. Some neurologists classify multiple sclerosis as the acute, progressive, and remitting forms depending upon the onset, course and outcome of the disease. In many instances, however, individual symptoms may be acute, slowly progressive or remitting in the same individual. Others classify the cases according to the predominant site of the disease, thus one may speak of a spinal form, a bulbar form, a cerebellar form, a cerebrocortical form. In most cases, however, the demyelinated foci are disseminated despite

the localized nature of the clinical picture.

Neurologic Findings. Since the disease foci are scattered throughout the central nervous system, the classical findings are: sensory involvement with stereoanesthesia, loss of vibration and position sense; motor involvement with paresis or paralysis of individual muscle groups; reflex changes with hyperreflexia of the deep and absence of some or all of the superficial reflexes combined with signs of pyramidal tract involvement; pallor of the optic nerve head indicative of degeneration of the optic nerve; ataxia, inco-ordination and difficulty in performing rapidly alternating movements (dysdiadokokinesia) indicative of involvement of the cerebellar or co-ordination system. These are the usual signs and symptoms in fully developed cases. An examination after one or more mild attacks with complete remission may fail to reveal any findings whatsoever and as a result the history is of utmost importance in making a diagnosis.

TREATMENT AND PROGNOSIS

A glance through the cumulative index under therapy for multiple sclerosis indicates in an instant the pleomorphic variety of treatments suggested and tried. For many years fever therapy with typhoid-paratyphoid vaccine and mechanically induced fever with the fever cabinet were in vogue. At a later date quinine sulphate was used rather extensively. Since the advent of vitamin B and particularly thiamine chloride, untold quantities have been poured into patients with multiple sclerosis via all routes. Of late the histamine and dicumarol treatments have become fashionable. In my opinion, the acute attack with excessive fatigue should be treated with rest, eradication of obvious foci of infection, and adequate diet. The status of the more recent therapies has not been fully analyzed or evaluated.

The prognosis in multiple sclerosis is not as grave as many would have the profession believe. Some individuals have two or more mild attacks and never go on to develop the advanced form of the disease. Others, of course, continue to have recurrent attacks with severe involvement of the nervous system followed by permanent defects of great magnitude. It is virtually impossible to prognosticate the status of the patient in ten or fifteen years following an initial attack of the disorder.

912 South Wood Street

Largest X-Ray Collection

Veterans Administration now is the custodian of more than 53,000,000 Army chest x-ray films of World War II veterans, which it will use in its long-range antituberculosis program.

The films, which include those made of each Army veteran at the time of induction and separation, comprise the largest group of x-ray films in the world.

The films will assist VA in its study of tuberculosis among veterans and will also be available for determining eligibility of veterans for compensation.

Chest x-ray films of Navy and Marine Corps personnel will be retained by the Navy. Those of Coast Guard personnel are in possession of the Public Health Service.

To augment study of the x-ray films, VA has established a "central case register" of all World War II veterans who were discharged from the armed forces because of tuberculosis.

This register enables the outpatient tuberculosis clinics of VA regional offices to keep in close touch with each veteran who contracted TB while in the service. Combined with the information on the millions of x-ray films, the register will be of assistance in the long-range study of the disease among the veteran population.

About 30,000 of these cases now are in the files. VA records show that about 23,000 veterans of World War II are drawing compensation for tuberculosis contracted in the service.

In addition to the Army chest x-ray films, VA also has on file the x-rays of all its patients and many of its employees.

All veteran-patients in general medical and neuropsychiatric hospitals are given chest x-rays at the time of their admission. If they remain in hospitals more than a year, they are x-rayed annually.

In addition, all patients reporting for scheduled medical examinations in out-patient clinics are given chest x-rays if they have not had such x-rays in the previous six months.

All VA hospital employees are x-rayed at the time of their employment and once a year thereafter. These examinations are done more frequently on personnel assigned to the care of tuberculous patients. Employees in regional and sub-regional offices who are in contact with tuberculosis sufferers are similarly x-rayed.

Doctors in VA's tuberculosis service estimate that more than 1,800,000 chest x-rays of patients and employees will be made during the current year.

——*Veterans Administration Press Release.*

CASE REPORT - - -

Two Cases of Foreign Bodies in the Bladder and Urethra

MARTIN J. LOEB, M.D.

NEW YORK, NEW YORK

Foreign bodies in the bladder and urethra are not uncommon. Foreign bodies may be left in the bladder and urethra inadvertently. Catheters, bougies, gauze, etc., are the objects introduced in this way; however, considering the many manipulations to which the bladder and urethra are subjected the number of foreign bodies introduced during treatment or operations is comparatively small. I have known, however, of a case where gauze packing was removed several months after having been left in the bed of a prostate.

Foreign bodies may find their way into the bladder through a fistulous tract between the bladder and an adjacent organ, i.e., the intestines or ovaries. The fistulous tract is caused by pressure necrosis of the contiguous walls. In 1846 von Ruge [1] reported a case of suppurative cystitis caused by a large amount of hair which found its way into the bladder from a contiguous large teratoma of the ovary. The treatment in 1844 was primitive and the patient died from general septicemia.

Foreign bodies may gain entry into the bladder and urethra as a result of trauma. Branham and Richey [2] recently reported a case where a Kirschner wire was inadvertently introduced into the bladder while nailing a fractured hip.

Masturbation is the most common cause of the introduction of foreign bodies into the bladder and urethra. Since the female urethra is short, that channel is an easy passageway for foreign bodies into the bladder. In the male, the urethra being longer, foreign bodies remain within that channel. The two cases here reported will illustrate that point. Exceptions, of course, do occur.

The literature abounds in reports of foreign bodies in the bladder and urethra introduced during the act of masturbation. The objects as well as the methods of introduction are as varied as the pathologic instincts of the individuals who insert them. Candles, lead pencils, bobbypins, iron bars, nails, glass cocktail mixers, have been observed. Bobbypins, because of their widespread use, the the most common foreign objects found in the female bladder. In 1918 Schwabe [3] collected from the literature 105 cases of foreign bodies in the bladder, of which 22 were hair pins. Gutierrez,[4] Gordon,[5] Augustus Riley,[6] Conzett,[7] Chenoweth,[8] Stabler,[9] Angel,[10] Boss,[11] Badenoth and Campbell,[12] and Hawkins [13] reported foreign bodies in the urethra and bladder. These references are but a few of the numerous reports in the literature.

REPORT OF CASES

CASE 1: L. J., aged 23, single, visited my office December 10, 1915. She was referred to me by Dr. Sarah S. Rifkin. The patient was x-rayed by Dr. I. O. Kassow who reported a bobbypin in her bladder.

The patient was a pale, anemic girl weighing about 110 pounds. She was extremely neurotic, restless and unable to remain still. Because of her extremely nervous state it was impossible to elicit a coherent personal history of previous emotional disturbances, of frustrations or of sexual phobias.

Previous to her coming to my office she visited another surgeon who advised a suprapubic cystostomy for the removal of this foreign body. This she refused to do because she wanted to keep the matter a secret from her mother. The possibility of an operation increased her anxiety to an almost psychotic state. Her story was that while sweeping the floor very vigorously with a broom she swept a bobbypin lying on the floor underneath her garments which found its way into the bladder. This, at least, shows that people who masturbate have imagination.

I made a cystoscopic examination in my office. I found the bobbypin was lying transversely in the bladder (Fig. 1). To take it out it was necessary to turn the pin around so that the smooth, round end would face the urethra. Several manipulations with the grasping forceps were necessary to accomplish this.

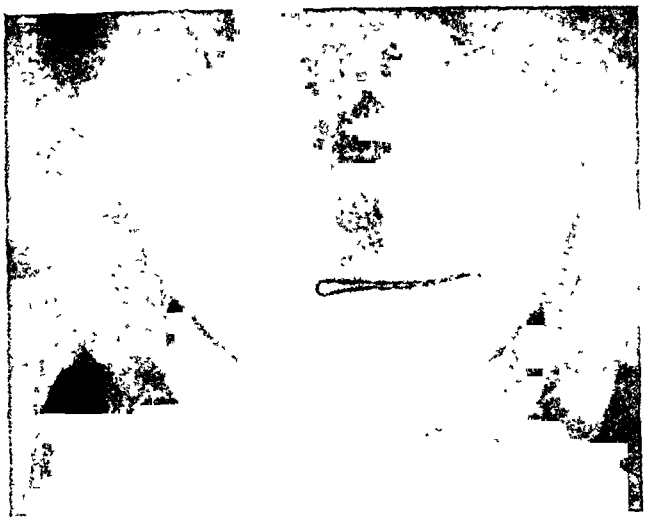


FIG. 1. X-ray of pelvis of L. J. disclosing bobbypin in the bladder.

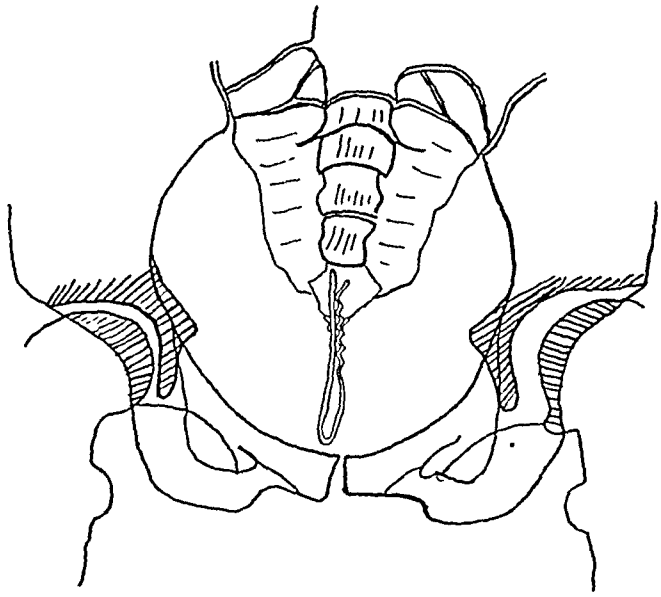


FIG. 2. Drawing showing bobbypin after it was maneuvered into position for removal.

The difficulty was that the pin assumed its original position the moment it was released from the forceps. The pin was finally brought around in a position for removal (Fig. 2) and the pin was removed. The pin was two inches in length.

I told this patient to return to my office within two days at which time I intended to take x-rays of her pelvis which would show the pelvis after removal of the pin. She, however, never returned to the office. Furthermore, she gave a fictitious name and address both to me and Dr. Rifkin to whom she stated she was referred by a patient.

CASE 2: H. M., aged 57, single, hospital number 166274, was admitted to the Bronx Hospital December 26, 1944.

The previous history was unobtainable because of reticence on the part of the patient and his refusal to answer questions coherently. He seemed to be a dull-witted individual and depended on his older sister, who seemed to dominate him, for guidance.

The day before admission the patient inserted a rubber tube taken from an enema bag into his urethra. On attempting to remove this tube, it tore off and part of it remained in the prostatic and cavernous portions of the urethra. To the interne the patient stated that he attempted to catheterize himself although he had no retention of urine and no difficulty in passing urine. To my questions as to why he inserted the tube into his urethra he remained silent in a defensive way.

The story that the tube tore in the urethra on his attempt to remove it seems quite improbable. It is my assumption that he cut off part of a rubber tube, four inches in length and one half inch in diameter, which he inserted into his urethra. On his attempt to remove it he pushed it farther inside. An object in the urethra will be forced in a centripetal direction. The introduction of a piece of rubber tubing, four inches in length and one half an inch in diameter, to the prostatic portion of the male urethra is an accomplishment of masturbation.

On admission the patient had a temperature of 106° F. with repeated chills. The rubber tubing in the urethra was not shown on an x-ray plate.

An attempt to remove this foreign body through the external urinary meatus was unsuccessful.

The patient was operated on December 27, 1944. A semicircular incision was made one inch above the anus. All the structures were dissected gently until the bulb of the urethra came into view. At this point the tube could be palpated in the perineum. An incision was made in the urethra anterior to the membranous portion. A tube about four inches in length and one half inch in diameter was removed from the urethra. The wound was sutured and a drain left there.

The temperature fluctuated after the operation from 102° to 104.5° F. On the fourth postoperative day the patient's temperature came down to normal. He passed urine through the urethrotomy for the first several days. Subsequently the urine was passed through the external meatus and through the fistulous tract. He was discharged on the 13th postoperative day at which time he passed urine normally through the urethra. The perineal-fistulous tract was almost healed.

SUMMARY

Two cases of foreign bodies are presented, one in the bladder of a female, the other in the urethra of a male. The difference in length of the male and female urethra is responsible for the difference in the location of these foreign bodies.

1882 Grand Concourse
Bronx 57, N. Y.

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MEDICINE IN THE NEWS - - -

CARONAMIDE

The concept of clearance by the kidney of substances presented to it by the renal blood supply can be applied to various drugs that are used therapeutically. For example, the reason for frequent dosages in the use of penicillin is the rapid rate at which the kidneys clear this substance from the blood stream. In fact, the overall clearance of penicillin at all plasma levels studied appears to be equivalent to renal plasma flow as measured by diodrast or *p*-aminohippuric acid (PAH). This means that some 1,200 cc. of blood per minute are cleared of penicillin. For this reason it is very difficult to maintain bacteriostatically effective levels of penicillin in the blood stream. Approximately 20 per cent of the blood or plasma penicillin is filtered through the glomeruli, whereas 80 per cent is excreted by the tubules.

Recent work on the use of drugs to inhibit the excretion of penicillin substantiates the tenet that tubular excretion is not simply a matter of passive diffusion but involves expenditure of metabolic work. It has been shown that large doses of PAH or diodrast will block the tubular excretion of penicillin. Therefore it is assumed that they all use the same tubular transport mechanism. Thus, if this mechanism is "saturated" by PAH at high blood levels, PAH is believed to competitively inhibit the excretion of penicillin, and adequate blood levels of penicillin can be maintained for longer periods of time.

Recently a new drug, caronamide, which is not excreted by the tubules, was found to block the tubular excretion of penicillin. Thus, caronamide must act on the same transient mechanism as PAH, but via another route. A working hypothesis is that the tubular transport mechanism is an enzymatic process utilizing penicillin as its substrate. It is further assumed that caronamide (used in much smaller doses than PAH) competes with penicillin for the substrate role, and thereby prevents the excretion of penicillin. This concept of competitive inhibition in enzyme systems has been nicely demonstrated in other biological phenomena. Thus, tubular excretion and also reabsorption are not passive processes nor are they "vitalistic." Tubular function involves osmotic work and probably the interplay of many undetermined enzyme complexes. The application of the clearance concept has been useful in furthering experimental investigation in this connection.

Cases from the Medical Grand Rounds Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

CASES 28 AND 29

ERYTHEMA NODOSUM

DR. PERRY J. CULVER: We are going to present the annual skin and medical grand rounds, and our topic will be erythema nodosum, with various aspects of the disease emphasized by the men who have had an interest in this problem. Dr. Perley will open the discussion by presenting the statistics of the hospital admissions on this disease.

DR. ABRAHAM I. PERLEY: This is a statistical study of all cases of erythema nodosum hospitalized at the Massachusetts General, the Baker Memorial, and the Philips House in the past ten years. These cases were hospitalized either because of the diagnosis of erythema nodosum or because erythema nodosum was a concomitant finding. In all, there were 56 cases so diagnosed. Seven of these cases were males and 49 were females. The youngest patient was two years old and the oldest 60. The following table indicates the age distribution of our cases (Table 1). In the age group between 20 and 40 there were 25 cases, constituting about 41 per cent of the total.

TABLE 1

Distribution of Cases by Age

AGE	NO. OF CASES
1–10	10
11–20	9
21–30	12
31–40	13
41–50	9
51–60	3

The distribution of the typical erythema nodosum lesions was as follows: Lesions on legs only, 26 cases; lesions on legs plus other areas, 52 out of 56 cases. There were only four cases in which the legs were not involved. Other areas of involvement were the thighs, buttocks, arms, and elbows. There was no involvement of the face in any of the cases.

Of the 56 cases, 49 had chest x-rays and of these, 35 apparently had negative x-ray findings. Twelve cases showed unusual hilar markings or hilar glands, and two of these were diagnosed as "possible sarcoid."

Biopsies of the erythema nodosum lesions were taken in only eight cases. Thirty-five of these cases had a diagnosis of erythema nodosum alone. In ten cases rheumatic heart disease was associated with erythema nodosum. Other associated diagnoses were made in 11 cases as follows: pulmonary tuberculosis, thyrotoxicosis, cervical adenitis, asthma, lupus erythematosus, pyelonephritis, appendicitis, intestinal obstruction, and ulcerative colitis, one case each; there were two cases with otitis media.

DR. CULVER: We will present two cases this morning, which are rather interesting in that they represent erythema nodosum in a mother and daughter. We will bring them in after we have reviewed their clinical history briefly.

The mother is Mrs. O., No. 567449, a 41-year-old woman who had joint pains involving most of her joints 12 years ago, at which time she was found to have badly infected tonsils. The tonsils were removed with relief of the joint pains. Following the tonsillectomy she had some red areas on her leg, which she said were hives. She was then in good health until November 1946, at which time she had a miscarriage at two and a half months of pregnancy, which was treated with a dilatation and curettage and penicillin.

In December 1946 or early January 1947 she had what was diagnosed as "virus flu." She had a temperature of 102.6° and received "sulfa" gum to chew during that episode. Two weeks later she developed the first of her skin lesions. These consisted of large, red, raised, tender nodules on the anterior aspects of both legs. They started in the latter part of January and since that time have run a cyclic course of two- to three-week periods, with recurrent crops of from two to five or six large, red lesions on the legs. They have been tender at first; later they have blanched and

assumed a purplish color with desquamation before complete disappearance. With the onset of each of these groups of lesions there has been a certain amount of malaise, chilliness, and, she thinks, fever at times, although she has not taken her temperature. She has had some suggestion of aches and pains in her arms, not limited to the joints. She has been placed on bed rest and has been treated chiefly with multivitamin capsules and aspirin. Her lesions have gradually cleared up until at the present time she shows only minimal residual signs.

X-rays were taken of her chest at an outside hospital and were reported to be negative. There has been no family history of tuberculosis.

The patient's daughter, aged 12, following a number of sore throats last spring, developed severely painful, red, raised, lesions on the anterior aspect of the legs. These lasted for several weeks and then disappeared. This spring she developed the same type of lesions without the antecedent sore throats. A chest x-ray at an outside hospital was reported as negative.

The mother's sedimentation rate has been elevated to a rate of 0.8 mm. per minute, corrected. Her hemoglobin, white blood cell count and hematocrit have been essentially normal. The urine has been negative. She has had a slight fever on one admission to the Outpatient Department.

I don't know how many can see the residual of one of the lesions on Mrs. O.'s leg. It is still a little indurated and there is a slight amount of purplish discoloration. She feels very much better and has had no aches or pains since she left her bed about a week ago.

Does anyone have any questions they want to ask?

DR. CHARLES L. SHORT: Did you mention the conjunctiviitis preceding each attack?

DR. CULVER: No. Preceding each outbreak of lesions on her legs she has had a conjunctivitis or injection of the sclerae which seemed to ebb and flow as the lesions on her legs did.

DR. PAUL D. WHITE: Any lesions in the mouth or throat?

DR. CULVER: No. Dr. Hill has been kind enough to bring some slides over and he is going to discuss the pathology of this condition and the pathogenesis and the etiology of the disease as seen from the dermatologic viewpoint.

DR. WILLIAM R. HILL, JR.: The lesions of erythema nodosum appear as symmetrical, tender, red nodules in the skin over the anterior tibia, buttocks, extensor surface of the arms and occasionally the face. They may or may not be accompanied by systemic disturbances. The number of lesions present varies from two to six and they range in size from one to five centimeters. They are discrete, rarely become confluent and almost never ulcerate. The latter finding is unusual in view of the fact that extensive thrombosis is seen in the cutaneous vessels in specimens removed for biopsy. The individual lesions disappear in ten days to two weeks leaving a bluish-black pigmentation at the site. New crops of lesions, however, continue to appear and prolong the attack for many weeks. Although no age is exempt, the greatest incidence in between 8 and 30 years. Females are affected seven times more frequently than males, according to data obtained from records of patients who have had erythema nodosum and who were observed at the Massachusetts General Hospital.

Most observers agree that erythema nodosum is a nonspecific reaction to a variety of infectious and toxic agents and is not a specific disease, although the latter theory was proposed by Lendon,[1] because of the definite clinical course and the occasional occurrence of epidemics. An organism thought to be specific has been isolated by Rosenow,[2] but Koch's postulates have never been fulfilled. Tuberculosis apparently is associated with the majority of cases observed in the Scandinavian countries. Wallgren reported that the incidence of positive tuberculin reaction approached 100 per cent, only 5 per cent of his 800 patients having had negative tuberculin reactions. Roentgenographic evidence of pulmonary involvement was also a frequent finding in these cases.[3] Punch [4] found in a number of student nurses undergoing regular tuberculin testing that the change from a negative to a positive tuberculin reaction was marked by the development of erythema nodosum. As an early manifestation of tuberculosis arising from direct contact with infected persons, erythema nodosum is stated to be second only to pleurisy. Tubercle bacilli have been recovered from the stomach washings of children with erythema nodosum [5] and Hubert [6] demonstrated the tubercle bacilli in the nodule itself. Because of the prevalence of rheumatic disease in England, cases of erythema nodosum seen there were ascribed to this cause. MacKenzie [7] reported a series of 108 patients with erythema nodosum, 17 of whom had associated swelling of joints and 10 others who had cardiac lesions. More recent studies have, however, demonstrated that true carditis is rarely seen in erythema

[1] Lendon, A. A.: Nodal Fever, London, Bailliere, Tindall & Cox, 1905.
[2] Rosenow, E. C.: J. Infect. Dis., 16:367, 1915.
[3] Wallgren, A.: Acta Med. Scand., 16:363, 1926.
[4] Punch, A. L.: Lancet, 1:10, 1911.
[5] Wallgren, A.: Am. J. Dis. Child., 41:816, 1931.
[6] Acta Dermato-Venerol., 21:499 (May) 1910.
[7] MacKenzie, S.: Clin. Soc. Trans., 19:215, 1886.

nodosum and that salicylates helpful in the rheumatic state do not influence erythema nodosum. By and large, tuberculosis and the rheumatic state have rarely been incriminated as the cause of erythema nodosum in patients who have been studied at the Massachusetts General Hospital.

In discussing pathogenesis, Lofgren [8] considers that the three most likely provocative factors are biologic, physical, and chemical. Included in the former are most bacterial diseases, the exanthemata, virus (lymphopathia venereum), spirochetal (syphilis), and fungus diseases, the latter of both the superficial (tinea capitis) and deep variety (coccidioidomycosis). Furthermore it has been demonstrated that bacterial antigens may act as accelerators of erythema nodosum. Sonck [9] reported seven cases of inguinal lymphogranuloma (lymphopathia venereum) in which an attack of erythema nodosum occurred. In three the attack was probably caused by the Frei test since it appeared when the local tissue reaction was at its height. The same findings have been recorded after the diagnostic use of trichophyton tests and after injections of tuberculin. Cases of erythema nodosum have been reported following surgical intervention of infected glands associated with lymphopathia venereum and following roentgen therapy to lymphomatous glands. Experience at the Massachusetts General Hospital has shown that numerous chemical agents may be associated with the appearance of erythema nodosum. This list includes bromides, iodides, arsenic, and sulfonamides. The last group of drugs has been studied extensively by Meischer [10] who reported 58 cases of erythema nodosum in patients following the administration of sulfonamide compounds, and noted that the eruption appeared on the second or third day following the initial dose in 30 per cent. Treatment with these compounds was continued in 17 patients, in all but five of whom the nodose lesions cleared up. Sulfonamides were given again to 25 patients after varying periods of time from a few days to several weeks. No fresh eruption was observed in 17. Examination of blood smears revealed no increase in eosinophiles and skin sensitization tests with the sulfonamides gave negative results; findings which he considered militated against the theory of drug allergy. He concluded, therefore, that erythema nodosum following the administration of sulfonamides, and this probably applies to other chemical agents, should not be interpreted as a drug rash, but that the part played by the chemotherapeutic agent was that of a provocator similar to, if not identical with, the Herxheimer effect observed in syphilis. In our experience there exists over and above those with the aforementioned causes, a number of patients in whom no etiologic cause is discovered after exhaustive study. Minimal study of a person with erythema nodosum should include examination of such usual constituents of the blood as the cells, chemical examinations (determination of drugs levels), the sedimentation rate, cultures, serologic tests, appropriate cutaneous antigenic reactions (tuberculin, Frei), and roentgenographic films of the lung fields.

In biopsy specimens removed there is evidence of a diffuse vascular disease. The vessels deep in the cutis are the site of the most marked involvement. The intima has been destroyed and the cells are shredded and lie free within the lumen. Within the vessels thrombi are seen, in various stages up to and including complete occlusion. A perivascular round cell infiltrate is noticable, among which large histiocytic cells appear. Within these fibrous nodules caseation necrosis is rarely seen thus distinguishing the granuloma from tuberculosis. Invasion of the fat results in Wucher atrophy.

DR. CULVER: I think we may leave all the discussion until the end of our comments. Dr. Short is going to discuss the medical aspects of this disease, particularly as related to the rheumatic fever and rheumatoid group.

DR. SHORT: Whatever the cause of erythema nodosum may be in an individual case, it is frequently associated with painful or swollen joints. There are various reports about the incidence of joint involvement giving a range of between 40 and 60 per cent, with about half showing actual joint swelling. In addition to the swelling we have seen joint effusion which has usually persisted for only a short time. It is necessary, of course, to distinguish a true arthritis from a painful lesion of erythema nodosum in the neighborhood of a joint, as well as from the edema of the ankles and legs which is sometimes found. The articular involvement is said to be more frequent in adult cases and in patients who have recently had streptococcic infections.

When we find a patient with erythema nodosum and joint involvement several considerations arise. First, are we dealing with a disease involving the joints, one manifestation of which may be the erythema nodosum syndrome? Among such diseases are meningococcemia, where the lesions are likely to be atypical, that is, more discrete and fewer in number and, perhaps, more often involving the upper extremities; and, rarely, cases of gonococcemia. Ulcerative

[8] Lofgren, S.: Acta Med. Scand., 122:175, 1945.
[9] Sonck, C. E.: Acta Dermat. Venerol., 21:473, 1940.
[10] Meischer, G.: Schweiz. Med. Wchnschr., 73:521, 1943.

colitis was mentioned as a disease that is occasionally accompanied by erythema nodosum, but some doubt has been cast on this association and one authority believes that we usually are dealing with subcutaneous pyogenic infections of low grade rather than true erythema nodosum. Coccidioidomycosis has been referred to. It must always be thought of in a patient who has been in an endemic area recently. Lymphopathia venereum has also been mentioned by Dr. Hill. This disease is occasionally associated with arthritis in the absence of erythema nodosum. Another condition which is sometimes difficult to distinguish is sarcoid, which may involve joints. Cases with positive biopsies for sarcoid have been reported showing typical erythema nodosum-like lesions, hilar lymphadenopathy and even diffuse infiltration of the lung fields. We must therefore be sure that we are not dealing with a specific infectious disease when we run into arthritis associated with erythema nodosum.

Next is the relationship of this condition to rheumatoid arthritis. I have gone through our files carefully and have found no case in which there has been a definite association of chronic rheumatoid arthritis with erythema nodosum. Nor have we seen any patient presenting this syndrome who has gone on to develop a chronic progressive arthritis. Of course, there is no reason why the two diseases should not coincide and, as a matter of fact, several instances of the coincidence of the two conditions have been reported. But certainly there is no reason to include erythema nodosum as a manifestation of rheumatoid arthritis or a disease having any close relationship to it. Incidentally, it is true that they both affect the female sex more frequently.

The relationship of erythema nodosum to rheumatic fever has already been discussed, including the fact that in the 19th century it was regarded as a definite rheumatic manifestation. More recently, the whole subject has been reviewed at great length by Keil.[11] For the controversial aspects of the subject I will refer you to that article. But, evidence of the association of erythema nodosum with active rheumatic fever with carditis seems to be very slight. In most of MacKenzie's cases there was little to show that the patient had any more than ordinary erythema nodosum with joint involvement or the coincidental finding of inactive rheumatic heart disease. However, there are a few well-described cases in the literature in which undoubted active rheumatic fever has been found in association with erythema nodosum or subsequent to it. Again, there is no reason why the two diseases should not occasionally coincide, especially since they both frequently follow an upper respiratory infection, usually caused by the streptococcus. Although the subject is still open to discussion, I would think that with the present evidence there is no reason to consider erythema nodosum a manifestation of rheumatic fever.

DR. CULVER: Dr. King is going to discuss the other great medical aspect of erythema nodosum, namely, the relationship to tuberculosis.

DR. DONALD S. KING: Dr. Hill has mentioned this aspect of the problem. If the theories held abroad are true, erythema nodosum is a manifestation of the first infection with tuberculosis. For example, a child with a negative tuberculin test and no previous exposure to the disease is exposed to a patient who is coughing up tubercle bacilli. In from three to eight weeks, if the exposure has been sufficient, that child develops a positive tuberculin skin test. With that skin test there may or may not be positive x-ray evidence of the primary infection (the typical primary lesion being in the lung itself and in the nodes which drain that portion of the lung). There may or may not be fever with the primary infection and there may or may not be erythema nodosum. When the erythema nodosum occurs, it is supposed, according to the theories, to be influenced by many factors: sex, the individual nature of the patient, the family tendency, and particularly, the country from which the patient comes. It is very definite in all the literature that the highest number of cases occur in Sweden, perhaps because of better observation. Drs. Waldon and James Alexander Miller, in Nelson's series of medicine, have a good article on this problem, and its occurrence in America as well as Sweden.

Erythema nodosum is therefore supposed to be evidence of allergy developing along with the development of sensitivity to tuberculin. The lesions are fairly typical allergic lesions and as Dr. Hill pointed out, not the lesions of tuberculosis; the few cases where tubercle bacilli are supposed to have been cultured from the skin lesion are, I think, open to considerable doubt. Waldron says he never found them and he has tried hard.

In Norway, Heimbech is the man who has made a special study of tuberculosis in nurses and these are his statistics. There were 700 nurses, 50 per cent of whom were tuberculin negative when they started working in the sanitarium. Of this total number 81 developed what he called tuberculosis. But erythema nodosum to him is synonymous with tuberculosis, and 16 of the 81 had erythema nodosum alone with no other evidence of tuberculosis; 44 had pulmonary tu-

[11] Keil, H.: Ann. Int. Med., 10:1686, 1937.



FIGURE 1.



FIGURE 2.

berculosis; 21 had pleurisy with effusion. Maybe he is right; it is a higher figure than we have.

Erythema nodosum has almost never been reported in Massachusetts in association with primary tuberculosis in children. I think it is possible that many cases may have been missed because erythema nodosum is the primary manifestation and the children might not have been seen at all in the early febrile stage when they develop these lesions.

In coccidioidal mycosis the same primary infection with erythema nodosum may occur.

There is a recent case in this hospital that is very interesting. It is exactly similar to the ones reported in Sweden. There was a child with a negative tuberculin test who was in the hospital for three months. She was exposed to an open case of tuberculosis and developed an unexplained fever. The chest was x-rayed and lesions were found consistent with a primary tuberculous infection. She then developed erythema nodosum. In the meantime, her lung process spread. That is exactly what is said to happen in Sweden, and I do not doubt that it happens here much more often than we think it does.

DR. ALFRED KRANES: Do the Scandinavians offer any explanation for the sex incidence?

DR. KING: Not that I can find anywhere.

DR. CULVER: I think the x-ray findings in this disease are almost unknown to many of the medical men. Dr. Robbins has brought over several x-rays and is going to discuss them.

DR. LAURENCE L. ROBBINS: This (Fig. 1) was a 32-year-old white female, No. 127087, who had a history of acute rheumatic fever three months before this film was taken, and here we see the more or less characteristic appearance that goes with erythema nodosum as seen by x-ray. You will notice that there is a more or less symmetrical hilar node enlargement, in addition, there is usually enlargement of the nodes of the right superior mediastinum, less commonly of the left. In the literature miliary lesions have been described scattered throughout the lung fields. I have never seen them for a certainty.

Here (Fig. 2) is a film taken approximately five months later and you will notice that the hilar nodes have diminished considerably in size. I think it is extremely important to realize that by x-ray this cannot be differentiated from sarcoid when it is in the stage of hilar node enlargement. Certainly, I think the miliary process throughout the lung fields is much more frequently seen with sarcoid.

Here (Fig. 3) is one that is, perhaps, even more striking. This happens to be a 25-year-old female, No. 519337. The first film was taken in February and the enlargement gradually disappeared (Fig. 4), so that these nodes appeared entirely normal eventually.

DR. KRANES: Was the condition associated with skin lesions, Dr. Robbins?

DR. ROBBINS: The patient entered the hospital because of red, tender, nodules over the shins and developed arthralgia while in the hospital. Some nodules also occurred in the forearms over the radial shafts. That is all the information I have regarding the clinical findings.

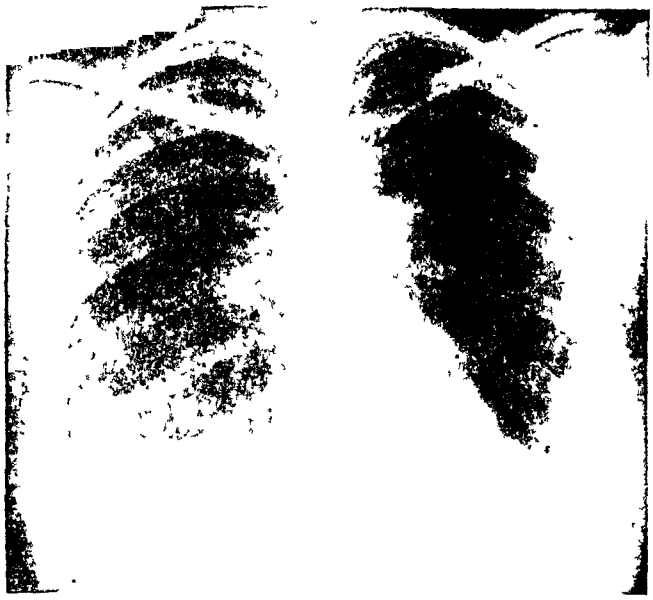


FIGURE 3.

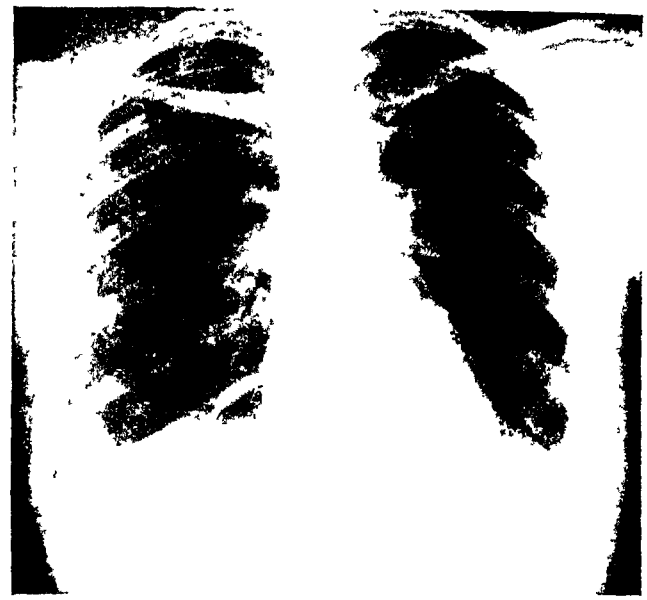


FIGURE 4.

DR. MAURICE FRLMONT-SMITH: If you have tuberculous glands, you would get evidence of pulmonary tuberculosis, wouldn't you?

DR. KING: That is what I was going to ask, how he knows that is not tuberculosis?

DR. ROBBINS: I was waiting for that. First of all, I think it is relatively rare to see quite so much symmetrical enlargement of the enlarged nodes with tuberculosis. Secondly, I am very skeptical about hilar node tuberculosis *per se* or mediastinal node tuberculosis *per se*. I think the reason this has been described so frequently is that films are not taken in the lateral projection and the lesion, located in the dorsal division of the lower lobe which may be the primary infiltrative process within the pulmonary parenchyma, is not recognized. I think there is confusion regarding that point. (These patients have all had lateral films, which I have not bothered to show.)

This is simply another instance of the appearance of the hilar node enlargement and its regression. I have often wondered if, perhaps, the reason that we have not seen the miliary process within the lung fields is that in the cases which we have observed, at least, it has not gone on for any great length of time. They have usually regressed rather rapidly.

DR. CULVER: In what percentage of the cases of erythema nodosum have you found the hilar nodes?

DR. ROBBINS: I think Dr. Perley answered that. He pointed out that it was approximately 25 per cent, I believe, of those that were x-rayed. Twelve of 56 patients had those findings.

DR. F. DENNETTE ADAMS: This is getting you into the clinical field and, perhaps Dr. King can answer it if you cannot, but can you get erythematous nodes set down on top of what we believe is sarcoid?

DR. KING: I would not want to combine the two. The problem is hard enough taking one alone.

DR. SHORT: Cases of sarcoid have been described with erythema nodosum-like skin lesions.

DR. KING: Confirmed by a skin biopsy?

DR. SHORT: A biopsy diagnosis of sarcoid was made. I am not sure about the erythema nodosum biopsy.

DR. ADAMS: But the patient had lesions like erythema nodosum?

DR. SHORT: Yes.

DR. ADAMS: Superimposed, if you will, on what was believed to be an underlying sarcoid?

DR. SHORT: Yes.

DR. CULVER: Dr. Bland, do you have any comments to make about this disease?

DR. EDWARD F. BLAND: Rheumatic fever has been implicated, as Dr. Short pointed out, for many years and we have seen a good deal of rheumatic fever during both the acute and the chronic stages of the disease. We have studied approximately 2,500 cases of young people and adolescents at the House of the Good Samaritan, and there have been half a dozen who at some time or other have had erythema nodosum. Furthermore, some of those patients were sent specifically for us to try to decide whether or not they had rheumatic fever. I recall only one that had some other suggestive evidence of active rheumatic fever and that was rather nebulous, namely, a long P-R interval. I concur with Dr. Short's summation that

a specific association between rheumatic fever and erythema nodosum has not been proved.

DR. CULVER: Dr. Lane, do you have anything you would like to say?

DR. C. GUY LANE: The other day I looked over the subject in connection with this symposium, and I was interested in a definition given 25 years ago, before a good deal of modern study was made, which I think was quite interesting. It described erythema nodosum as an inflammatory effusion, not saying an infection or disease, but an inflammatory effusion characterized by the formation of variously sized, rounded, more or less elevated, tender, erythematous nodes and swellings, mostly on legs, and attended with a variable degree of systemic manifestations. It seems to me that sums it up very well indeed, concluding with the systemic manifestations which we have heard described very well here today by Drs. Short, King, and Robbins.

DR. CULVER: Is there anyone else who has any comment to make?

DR. SHORT: I would like to ask a question. Do you ever see the x-ray picture such as you have shown here of erythema nodosum, occurring in upper respiratory infections without skin lesions? In other words, could the hilar gland enlargement be secondary to the precipitating infection rather than to the syndrome of erythema nodosum?

DR. ROBBINS: I am not acquainted with it in upper respiratory infection, are you, Dr. King?

DR. KING: No, I am not.

DR. ROBBINS: I think there are three conditions in which you may see its (the x-ray picture of erythema nodosum) occurrence with relative frequency. They are sarcoid, metastatic malignancy, and erythema nodosum. You may also note a somewhat similar appearance with some of the pneumoconioses.

DR. FREMONT-SMITH: How about lupus?

DR. ROBBINS: I have not seen enough of that to have much of an opinion on it. In the literature a process has been described throughout the lungs with involvement of the lymph nodes which, I think, would be difficult to distinguish.

DR. WHITE: Dr. Hill, do you have any suggestions about therapy?

DR. HILL: No.

CASE 30

COOLEY'S ANEMIA

DR. EARLE M. CHAPMAN: We are going to present a case which we think is one of probable blood disorder. We can't offer a triumph in therapy because if we are correct in our diagnosis, so far as we know there is no therapy for this disorder, because of the fact that the fundamental pathologic physiology of the disorder is unknown.

This is a case of what might be called Mediterranean Cooley's anemia in an adult. It is usually thought of and recognized as a disease of childhood, leading to early death. There are certain characteristics of the blood that make this disorder diagnosed rather easily, I believe, with or without sternal puncture.

The patient is a young Italian from Augusta, Sicily, who has a history that Dr. Peterson will present to you in a moment. The disagreement in diagnosis will be quite evident. I have held fast to this diagnosis, despite the opposition. Despite some of the variations from the usual picture, I think he has it.

DR. EDWIN M. PETERSON: Mr. S., No. 120099, a 44-year-old candy maker, came to the hospital on July 11, 1947, complaining of intermittent attacks of chills and fever for 20 years. As a boy in Sicily, at the ages of 13 and 15 respectively, he had bouts of severe, shaking chills and fever, lasting one week, diagnosed as malaria and treated, apparently successfully, with quinine. He came to this country at the age of 17 and has had no further known malaria.

However, seven years after he came here, or about 20 years ago, he began to have recurrent episodes which followed a pattern something like this: he would have aches and pains in the backs of his legs and across the soles of the feet, which would progress to the lower back and be so severe as to put him to bed. These were accompanied by fever and chilly sensations, without actual shaking chills. He would go to bed for two or three days, the fever would vary between 101° and 102°, and would then subside spontaneously.

These attacks have occurred two or three times a year over the last 20 years. He has been to various doctors, clinics, and hospitals, without ever having a definite diagnosis made. He was at this hospital in 1943, where a diagnosis of atypical pneumonia was made and substantiated by x-ray findings. At that time, the spleen was found to be enlarged. He was discharged, however, without any attempt having been made to explain the enlarged spleen. One smear examined for malarial parasites was negative.

Since his discharge, he has been followed in the Outpatient Department at infrequent intervals, and has continued to have attacks of chills and fever. Last fall, they became more frequent, occurring once a month over the course of the winter; then they began occurring every two weeks. Finally, because he was

losing so much time from his work, he sought admission again, in an effort to find out what was wrong.

On admission, his physical examination was entirely normal, except for the fact that he was blind in one eye, due to an old separation of the retina, and had an enlarged spleen, felt four fingers below the left costal margin, rather soft and nontender.

TABLE 2

Laboratory Findings

Blood
RBC: 5.40 million
WBC: 8,000
Differential: Polymorphonuclears 66, lymphocytes 28, monocytes 2, eosinophils 4
Hemoglobin: 12.9 Gm.
Group: O, Rh positive
Sedimentation Rate: 0.5 mm./min.

Fragility Test	Began	Complete
Patient	0.36%	0.32%
Control	0.40%	0.36%

Brucella and Widal Tests: Negative
Smear for Malaria Parasites: Negative
Van den Bergh: 0.8 mg.% direct; 0.9 mg.% indirect

Stool
Guaiac Test: Negative

Urine: Normal
Urobilinogen: Normal (1:10)

His laboratory work is shown in Table 2. His smear has been described as showing slight variation in size and shape of the red blood cells, with many target cells and occasional stipple cells. When seen in the Outpatient Department at one time, during an acute episode, his white count was 16,000, and there were a large number of stipple cells in the smear, as many as two or three per high power field. Differential counts were essentially normal. There were repeated thick and thin smears for malaria, which were checked at the Medical School and no parasites were found. There was some increased resistance to hemolysis of the red blood cells as shown by the fragility test.

Since he has been in the hospital, his course has been afebrile, with no repetition of his typical attacks. We have never actually seen him in one. The white blood cell count has remained normal. Smear and hemoglobin have remained unchanged. However, his spleen is still enlarged and Dr. Chapman has made a diagnosis of Mediterranean anemia, although other observers do not think the anemia is severe enough to account for his symptoms.

In regard to his family, I might say that he has three boys and one girl whom we have had come into the hospital in order that they might be examined. None of them has an enlarged spleen. The three younger boys have a slight degree of anemia, with target cells present in the smears. The youngest boy, age five, has a hemoglobin of 8.5 Gm., and has been studied in the Children's Medical Department, where a diagnosis of rheumatic fever was made in the past, but not proved. *An older daughter of 17 is completely* normal. There is one older brother who also has a history of questionable malaria in Sicily. He has a palpable spleen, no anemia, but target cells in his smear.

DR. CHAPMAN: They are going to bring him in in a wheel chair, but he can walk, as he has no complaints except for the recurring bouts of fever over the past 20 years, which I believe are part of the syndrome of Mediterranean anemia in an adult.

Some of you may remember a similar case that I showed here three years ago; the woman who had alternated between a diagnosis of malaria and tuberculosis, and had spent time in a tuberculosis sanitarium. So far, this man has not been confined to a sanitarium, but the diagnosis of tuberculosis as well as rheumatic fever have been entertained by others for years.

DR. WYMAN RICHARDSON: Did you say that sickling had not been demonstrated?

DR. PETERSON: It was looked for by the technic of a sealed hanging drop overnight and not found. Not by equilibration with carbon dioxide.

DR. CHAPMAN: He has been given adrenalin to bring out the parasites of malaria, but this did not reveal them.

I might say that I was not familiar with the possibility of this diagnosis, really, until 1943, when van Ravenswaay [12] reported such a patient in the *Journal of the American Medical Association,* a boy who came from a town in Sparta, Greece. The story was one of recurrent chills and fever. A good bit of detail was obtained from this single patient. For instance, the patient apparently said that in Greece, there was a well-recognized disorder that was confused with chronic malaria. The Greeks called it *ellodous peretous* which was the word for this fever, familial in origin, which usually led to early death in infants; but if they reached adulthood, and reproduced, their children in turn, might have the disease. The Greek word for true malaria is somewhat the same, *elodus peretos.*

Van Ravenswaay brought out this similarity of the diseases and the fact that the diagnosis is established more or less by exclusion of malaria. Thus we felt justified, having done all of these studies, in putting the patient on a course of atabrine over a long period

[12] Van Ravenswaay, A. C., K. H. Schnepp, and C. Moore: J. A. M. A., 122:83 (May 8) 1943.

of time, and observing him, to see if the fever cleared up. That is our next plan. I would welcome Dr. Dameshek's remarks on this case and his opinion.

DR. WILLIAM DAMESHEK: I want to congratulate Dr. Chapman upon the correctness of the diagnosis.

We have been doing a lot of marrow studies in these cases as part of a project for the study of these Mediterranean anemias and we believe that most cases show the signs of a definite disorder of red cell production, which probably centers around a defect in hemoglobin metabolism. At the present time we are engaged in a series of studies: genetic, chemical, bone marrow and hematologic; it is the hope that we may learn something about the disease.

Our first experience [13] with the relatively mild cases of what has been called Cooley's anemia was reported in 1940, three years before van Ravenswaay's report. This was reported as a case of "target cell anemia." The patient, Joe C., was a boy of about 21 years of age who showed anemia, splenomegaly, slight jaundice, and marked bone changes. The anemia was hypochromic with many target cells and increased resistance of the red cells to hypotonic salt solutions. Since he was 21 and had no nucleated red cells, we felt that he represented a relatively mild variant of Cooley's anemia. We then began to see still milder cases [14] and we reported upon them in 1942 and 1943. We are now engaged in a long-term comprehensive study of the various facets of the disease.

There are a great many mild cases. The disorder is familial and hereditary. The mild cases are transmitted by either the father or the mother as a mendelian dominant characteristic. If either the father or the mother is affected, the majority of the children have the disease. The severe forms known as Cooley's anemia are transmitted by both parents, both of whom have the mild disease. These statements were first made in 1942 and have been confirmed by Valentine and Neal of Rochester, New York.[15]

In the severe Cooley's anemia which is transmitted by both parents, the child is in all probability homozygous for the trait. The mild disease may take many forms. The outspoken cases of Cooley's anemia occur in the young, and these patients die before the age of 12 as a rule. They are very anemic, very icteric, with the spleen enlarged; the bone changes are very striking, and the blood shows target cells, oval cells, stipple cells, and nucleated cells.

Joe C. showed much the same features except that he did not have the nucleated red cells and furthermore was 21 years of age.

The next most severe type of case is an individual who is moderately anemic, slightly icteric, with splenomegaly present, but with or without bone changes. These cases show moderate anemia and target, oval, and stippled cells.

The mild cases are not recognized clinically, but are usually observed by studying families or perhaps are found more or less accidentally by studying an Italian who has a stippling of the red cells and in whom the question of lead poisoning has come up. Or, if you are taking care of a young woman of Italian origin who presents hypochromic anemia refractory to iron therapy a look at the blood smear shows target, oval, and stippled red cells. These mild cases may have a slight anemia or they may have no anemia at all. In some of the cases, as in the patient presented, the hemoglobin may be 70 to 85 per cent, and the red blood cell count six to seven million. In other words, there is a hypochromic erythrocytosis. These cases have no splenomegaly, no bone changes, but they do show the target, oval, and stippled cells. These mild cases may show many target cells and few oval cells, or many oval cells and few target cells, or many stippled cells with few target or oval cells.

We have been doing some interesting hypotonic fragility studies with the photoelectric apparatus and have been demonstrating a very interesting type of fragility curve. The red cells break down in different amounts in varying degrees of salt solution and have a very broad base of breakdown indicating an abnormal type of red cell production by the bone marrow and a very heterogenous type of red cell population in the blood.

The mild cases go along absolutely without symptoms and without signs. They look normal. But they may beget cases just like it in their children, or if two of them are mated, then Cooley's anemia may occur. These mild cases occur, according to the statistics of Valentine and Neal, in one Italian out of 25, which is a fairly high percentage. Is that right, Dr. Limentani, in our cases?

DR. DAVID LIMENTANI: Five or six per cent.

DR. RICHARDSON: I would say you would find changes in at least 25 per cent of our Italian population.

DR. MAURICE FREMONT-SMITH: What about the attacks of fever? Are they a part of it?

[13] Dameshek, William: Am. J. Med. Sc., 200:445, 1940.

[14] Dameshek, William, Tibor J. Greenwalt, Russell J. Tat, and Camille Dreyfus: Hemolytic Syndromes. Exhibit, American Medical Association, 1942. Privately printed.
Dameshek, William: Bull. N. E. Med. Center, 4:67, 1942.
Dameshek, W.: Am. J. Med. Sc., 205:643, 1943.

[15] Valentine, W. N., and J. V. Neel: Arch. Int. Med., 74:185–196 (Sept.) 1944.

DR. DAMESHEK: These cases occur in six to eight per cent of all Italians. It is a good possibility that two Italians who have this trait may marry, because six to eight per cent have it and those Italians may beget either cases of Cooley's anemia, or moderately severe cases, or mild cases, depending upon how the genes mix up, apparently.

Now about the question of fever and febrile attacks with jaundice. I would say that I have never seen a hemolytic crisis in these cases. It must be very rare.

DR. ALLAN M. BUTLER: That is the chief complaint of this patient.

DR. DAMESHEK: None of my cases of this type, as far as I remember, has had attacks of chills and fever. Is that right, Dr. Limentani?

DR. LIMENTANI: Not one.

DR. DAMESHEK: It must be extraordinarily rare. A hemolytic crisis may occur in sickle cell anemia. It occurs in the spherocytic type, but not in the Mediterranean type. If you have attacks of fever, you have to think of something else.

DR. BUTLER: If you put this fellow on a suppressive malaria therapy, I think it would be nice not to use atabrine, but to use one of the newer forms of suppressive therapy that does not cause the yellow coloring and that also does not cause so many of the side symptoms.

DR. CHAPMAN: Within six months to a year, we hope to report whether or not he has had further febrile attacks after a course of antimalaria treatment.

DR. RICHARDSON: We had a patient on the Children's Service and the question came up, whether he had rheumatic fever or Cooley's anemia. He had a blood picture that would go with the Mediterranean anemia. He actually turned out to have a tumor of the bone.

DR. DAMESHEK: I should like to add two other little points: One is that these children, even with the relatively mild cases, may have a systolic murmur of the heart simulating rheumatic heart disease such as one sees in sickle cell anemia, and because a good many cases have that, they are classified as rheumatic heart disease. The other point is that one always has to rule out sickle cell anemia and the only way sometimes to distinguish a mild case of sickle cell anemia from the Mediterranean disease is by the sickling test.

CASE 31

ARGYRIA

DR. HELEN S. PITTMAN: This case is a man who, we think, demonstrates that things aren't always what they seem. He was sent into the hospital with an admission diagnosis which we think has been changed properly to something else at the present time. Dr. Kelley will present the case.

DR. RITA M. KELLY: Mr. P., No. 539212, is a 61-year-old draftsman who entered the hospital on June 6, 1947 via the Outpatient Department.

The history began at the age of 17, when he was rejected by the Navy because of the finding of an irregular "tobacco heart." Up to that time, he had had no symptoms of any cardiac disorder. He had no symptoms until the age of 20, when he developed episodes of severe palpitation, accompanied by loose mucous diarrhea and occasional vomiting. These attacks were so incapacitating that he was unable to work for three or four years, but symptoms gradually subsided spontaneously. He was seen at that time at the Boston City Hospital and was told that he had mitral murmurs. He was perfectly well until the age of 45, when he had a recurrence of attacks of palpitation, accompanied by diarrhea and vomiting. His blood pressure the first time was elevated, but he maintained a systolic level of 160 to 190 on repeated examinations. At this time, too, because of his digestive complaints, he was given a stomach preparation, containing among other things, bismuth and silver nitrate in dilute solution. He took this for several months, possibly several years.

He did well then, until the age of 55, seven years ago, when again he had a recurrence of the symptoms, this time accompanied by considerable fatigue and weakness, forcing him out of work for a few months. His palpitation was much less marked during this period. He was given additional medicines for blood pressure, which was at this time 200/100. For the past 18 months, he has begun to have headaches, beginning in the temporal area, and radiating up over the head and down in the occipital area. These have increased and recently were accompanied by marked fatigue and weakness, which forced him to give up work entirely eight months ago.

Throughout the past years, he has had attacks of sinusitis, and has taken a variety of preparations of nose drops, including Argyrol. He believes that he has used a half-ounce bottle every six months, on and off, during the past several years. Since the age of 17, he has seen a score of doctors, always presenting them with the peculiar cardiac problem, challenging them to make a diagnosis. He has had an amazing variety of diagnoses made; congenital heart disease; insufficiency of the mitral valve; insufficiency of the aortic valve; essential hypertension, etc.

The number of doctors he has had and the number of diagnoses made, have been exceeded only by the

number of medicines he has taken. These have included all sorts of stomach preparations: bismuth and silver nitrate; copious quantities of phenobarbital, and triple bromides, and chloral hydrate, at various times. In addition to this, all known patent preparations for sinusitis.

He was seen in the Outpatient Department a couple of weeks ago, where the observer was struck by the slate-gray color of his face, and his wife says this color has been present for about four years. He doesn't recall having noticed it particularly, except in the finger nails, which he thinks are a little bit blue and have been blue for many years but he is not sure just how long. His blood pressure has been 270/150. No pressure was obtainable in the legs. No dorsalis pedis pulses could be found on the feet.

On this basis, diagnoses of coarctation of the aorta and argyria were made, and the question of methemoglobinemia was raised. He was admitted to the House for study. Upon admission we found a small, thin, man possessor of a mass of medical misinformation, which he would dispense at the slightest urging. He had a peculiar slate-gray color to his face, which was prominent over the forehead and scalp, and which did not blanche on pressure. He had the same color in the finger nails most predominantly around the moons. He was amazingly benign looking, considering the blood pressure of 200/127 in one arm and 270/120 in the other arm.

There were no palpable or observable vessels in the intercostal areas. The heart was slightly enlarged to the left. There was a systolic murmur and a soft diastolic murmur along the left sternal border which was audible at the apex. These murmurs almost have disappeared since he has been in the hospital although they apparently were quite pronounced on admission to the Outpatient Department. He does have a faint diastolic murmur along the left border of the sternum. The abdomen and extremities were negative. He has a definite left dorsalis pedis pulsation; there is no clubbing of the fingers. There is nothing to suggest a congenital cardiac lesion. His work-up since he has been in, reveals that the hypertension has had little effect on his cardiovascular and renal system. In general, the kidney function is, so far, within normal limits, with a concentration of 1.020. Electrocardiogram reveals a slight left ventricular strain. Chest x-ray reveals no enlargement of the heart whatever.

During the hospitalization he has continued to run a systolic blood pressure of 260 to 210. He has had one headache while he has been on the ward, which was readily taken care of by aspirin. Aside from that, he has been asymptomatic completely.

Biopsy of the skin of the forehead, unfortunately, is not ready yet so that confirmation of the diagnosis of argyria cannot be made yet.

Out of this mass of data, we have come to the diagnoses of essential hypertension of benign variety; argyria and severe cardiac neurosis.

DR. PITTMAN: The artificial light in this amphitheatre is not ideal for his coloring, but I think that you can get an idea of the skin color. If you get the light properly I think you can see very clearly the discoloration which begins at the distal portion of the nail and is most marked at the bases.

DR. JAMES H. MEANS: Does it get into the folds of the skin and the palms of the hands, like Addisonian pigmentation?

DR. PITTMAN: According to Dr. William R. Hill, it is extremely rare.

DR. LAURENCE L. ROBBINS: Certainly there is nothing that is very striking on this film. The only thing even suggesting hypertension is some rounding of the apex of the heart. I don't believe that that is particularly unusual for his age. There is no evidence of notching of the ribs. His lung fields are perfectly clear.

DR. PITTMAN: What about his heart today, Dr. White?

DR. PAUL D. WHITE: It seems normal. He must have had only transient hypertension, through all these years. I suppose that if we took his pressure when asleep, it might be normal.

DR. WALTER BAUER: Why do you say that, Dr. White, when he has had an elevated pressure for 20 or 30 years?

DR. WHITE: As a rule, such patients don't have sustained hypertension day and night.

DR. BAUER: You see them in your office with high pressure.

DR. WHITE: That is a different story. You are then getting a pressor reaction. The degree of strain depends upon what percentage of the 24 hours the pressure is raised. With only a few hours a day of hypertension, you may do very well, although even a transient hypertension may be serious. I would think that in all probability for the most of the 24 hours each day, his pressure has been quite good. When a doctor comes to take his pressure, however, or if even a nurse takes it, it is up a bit; hence I think he ought to have his pressure taken when he is asleep.

DR. MEANS: How do you manage to do that?

DR. WHITE: You can have the blood pressure cuff already on the arm when he goes to bed. I have measured the pressure of people asleep, without waking them up.

DR. BAUER: I don't see what right you have to postulate that he has a normal blood pressure, when asleep, or 22 hours of the 24.

DR. WHITE: Except that when we investigate, we find that it is often so. His diastolic pressure frequently has been found to be 120 to 130. I don't believe you can have a diastolic pressure of 120 or 130 for 20 or 30 years, without its doing harm. From our experience with such cases, there is trouble sooner than that.

DR. BAUER: I can think of one diabetic lady who has had hypertension of this grade for 30 years without demonstrable cardiac enlargement.

DR. WHITE: Those cases tend to have relatively high systolic pressures but not such high diastolic. This man probably hasn't had a high diastolic pressure for a long period of time. We ought to talk more about the diastolic pressure in our cases, and less about the systolic pressure, which is relatively unimportant.

DR. PITTMAN: This man has taken up beds in hospitals recurrently for the last 40 years and everyone has thought he was a fascinating problem of differential diagnosis.

DR. BAUER: This case illustrates very well the harm that can be done by physicians. Not infrequently poor advice causes illness and disability sometimes leading to complete invalidism.

DR. PITTMAN: That is right. His work is that of a draftsman not a laborer. Drs. Hill and Pillsbury in their monograph on argyria point out that the line on the gums is commonly thought to be the initial lesion but is found in only ten per cent of the case studied, and they had studied all the reported case in the literature. The various portions of the face are really more important and it is the forehead and temples, and the nose that are the most important. I never happened to run into silver nitrate as a gastric medication, but apparently it has been used extensively.

DR. MEANS: Yes, and they also used to use it as a treatment for ulcerative colitis, as an irrigation.

DR. WHITE: One of the most striking patients that I have seen with argyria was a youngster in whom had been mistaken for congenital heart disease. The patient came up from the south to have considerati as to what congenital defect was present. She h always been very much restricted in activity althc she had been perfectly healthy. She was a little and was still taking nose drops when I saw her. (of the easiest ways to identify her argyria was to h her run up and down a flight of stairs whereupon .e color improved greatly, the pink coming out and c ering the argyria; this exercise would have increas the cyanosis if she had had the morbus caeruleus (c anotic type of congenital heart disease).

Editor's Note

The skin biopsy reported subsequently confirmed the diagnosis of argyria. The patient was discharged without further treatment.

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Diagnosis for Quiz Case: Disseminated lupus erythematosis.

The Treatment of Coronary Artery Disease*

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The treatment of coronary artery disease is, of ,ourse, the treatment of coronary atherosclerosis and : complications. The regimen of active treatment ,most diseases should be preceded by a consideration ;revention. Unfortunately at the present time this ·roach remains largely of hypothetical interest. So h/ factors are involved in the production of coro- ;y atherosclerosis, that it is impossible to control all ro' them. Race, heredity, inherent disturbances of .olesterol metabolism and many other imponderables ay determine the time of appearance and the rate of rogression of the atherosclerotic process. It is impos- ble to predict, save by generalizations, in which indi- iduals coronary atherosclerosis will develop, and for vhom preventive measures should be considered. A :omposite prototype of the individual who should be expected to develop coronary arterial disease would be a heavily smoking, diabetic, hypothyroid, white male, who had a dietary predilection for eggs and other dairy products and whose father had died of angina pectoris at the age of 50. The antithetic type would be a nondiabetic, nonhypothyroid, female Chinese who ate very little cholesterol-containing foods and among whose ancestors were many octogenarians. Preventive measures would prove mandatory in the former instance and unnecessary in the latter. Among the thousands of individuals with average habits and heredity, it is difficult to identify those who will develop severe coronary artery disease. However, in families with a high incidence of cardiovascular disease, it is certainly a duty of the physician to point out to the members of that family what we do know about the determining factors of coronary atherosclerosis. The role of faulty cholesterol metabolism as a causative factor is an alluring one, but the precise method of dietetic control in the patient without endocrine disease is not specifically known. In diabetic or hypothyroid patients, careful control of each disease is, in a way, a specific preventive measure by reduction of the hypercholesteremia and by correction of faulty lipid metabolism. The prevention of the progression of atherosclerosis by decholesterinizing agents such as choline, and methionine is an encouraging approach, but as yet is not definitely established. The interdiction of smoking is perhaps a positive preventive measure. The effect of tobacco is certainly not beneficial, but its exact quantitative effect has not been evaluated.

The active treatment of coronary artery disease begins when the pathologic process is indicated by the clinical signs and symptoms of myocardial ischemia, usually angina pectoris. The pain may occur spontaneously in the course of ordinary daily activity or, as part of a diagnostic measure, it may be induced in latent cases by the exercise tolerance test [1] or the anoxemia test of Levy.[2] When coronary artery disease becomes obvious it is well to visualize as accurately as possible the condition of the coronary arteries in that individual. This will serve to indicate what can be accomplished and what cannot be accomplished by treatment. We are interested in knowing the degree of the atherosclerosis, the diffuseness of involvement, the number of occlusions, the extent of collateral circulation, and the presence or absence of previous infarctions. The work of Blumgart, Schlesinger, and Zoll [3] has enabled the clinician to predict with fair accuracy the condition of the coronary arteries in the various clinical syndromes resulting from coronary atherosclerosis. In the majority of patients in whom angina is the first cardiac symptom, old complete occlusions have occurred in at least two of the three main coronary arteries. These are the patients without valvular heart disease or arterial hypertension. Angina pectoris occurring in patients with aortic stenosis or arterial hypertension is associated with less extensive coronary artery disease. In the patients who developed angina following congestive heart failure from valvular heart disease, Blumgart and his co-workers found coronary sclerosis in only two of nine patients. Such angina, therefore, is not associated with significant coronary atherosclerosis. In the patients with no extra heart load, without hypertension or

* Given as a lecture at the Postgraduate Course of the Amerian College of Physicians at Los Angeles, February 1947.

valvular disease, the demand for coronary blood is relatively small and the coronary circulation has to be markedly impaired before ischemia develops. The demand for blood by the heart with the load of valvular heart disease or arterial hypertension is enough greater that ischemia and angina will develop with much less impairment of the coronary circulation.

It is apparent that by the time primary angina pectoris develops the clinician is confronted by a formidable problem. The coronary circulation has probably compensated already for one or two complete arterial occlusions. The larger arteries are so sclerotic that they can dilate little of any. Diffuse intercoronary anastomoses, however, have been produced by the slow throttling of the coronary circulation. The atherosclerosis is so diffuse that it would seem that the coronary reserve was probably exhausted. Clinically, however, patients are seen who despite severe angina pectoris and with only slight change in their ordinary activity gradually improve and live for many years. This can be explained most logically by the development of even further anastomoses. The reflex production of angina by cold, or viscus distention, occurring without any increase in heart rate or in blood pressure, certainly suggests that there is a considerable reserve anastomotic network which can be affected reflexly with resulting vasoconstriction and myocardial ischemia. If it can be reflexly stimulated to produce angina, it can be theoretically kept dilated to prevent ischemia. This potential reserve collateral network represents the target at which treatment must be directed. The development of the network to the maximum must be encouraged and reflex vasoconstriction must be avoided. The most effective stimulant to the development of collateral circulation is the slow narrowing of the coronary arteries producing continuous slight ischemia insufficient to produce other than minute tissue necrosis but adequate to stimulate anastomosis. The fundamental objects in the treatment of coronary artery disease, therefore, would seem to be first, to promote the development of the maximum collateral circulation and to maintain its maximum vasodilatation. Second, to reduce the load upon the heart muscle which increases the demand for coronary blood flow. Third, to avoid any sudden disproportion between demand and supply of the blood, inducing cardiac catastrophes. The constant concern must be to prevent marked ischemia with necrosis of the heart muscle. Since marked ischemia for a relatively short period may produce necrosis or death this should be guarded against and all measures should be directed against it. What help can we expect from drugs in improving coronary circulation?

EFFECT OF DRUGS

A vast amount of work on animal and man has been done. Despite the experimental work which has demonstrated an increased coronary blood flow following the use of various drugs, clinicians in general have been more disappointed than elated in their observed effect upon the patient with the exception of nitroglycerin. Because of species variation, the result of animal experimentation must be cautiously evaluated Experimental conditions are too abnormal to accept the results by analogy as necessarily significant of what may occur in man. The chief objections in addition to the species difference, are the determination of the drug effect upon normal arteries, and the use of large doses of drugs which are not applicable to man. One determines what happens to a dog with good arteries under abnormal conditions with a large dose of a drug, and attempts to predict what would happen to a man with poor arteries, under different conditions, with a relatively small amount of the drug. These objections apply to the studies of the xanthines in dogs and cats. Despite these objections, the recent work of Mokotoff and Katz [4] is encouraging. They ligated the left descending anterior artery of the dog, gave aminophylline for eight weeks, and then compared the size of the infarcts with those of control animals. The average size of the infarcts in the dogs given aminophylline was definitely smaller. The dose, however, was one impractical for man. It would be the equivalent in a 70-kilogram man of 15 gr. intravenously the first day, and then 15 gr. twice a day by injection for seven days and 15 gr. daily in the muscle for seven weeks. Similar objections apply to the use of papaverine. The same experiment was performed and the infarcts at the end of eight weeks were smaller than those in the control dog. The equivalent dosage of papaverine in a 70-kilogram man would be a little over 5 gr. intravenously the first day, 5 gr. twice a day subcutaneously for seven days, and then 5 gr. daily by injection for seven weeks. When given in the dog in doses equivalent to that found in man (the dosage was 1.15 to 1.6 mg. per Kg.), Essex and his co-workers [5] found that the drug improved coronary flow for only two to three minutes. Atropine has been shown to have a strong effect in preventing fatal reflex vasoconstriction in dogs following ligation of a coronary vessel, but the preventive dose was 0.1 mg. per kilogram intravenously, an impractical dose in man.

Evaluation of Drugs by the Exercise Tolera Test and the Levy Anoxemia Test

Evaluation of the efficacy of drugs by the clinic

ınd subjective response of the patient is notoriously unreliable due to the spontaneous periods of improvement and relapse of the disease. The results obtained by these methods are usually not convincing. Two studies are available based upon responses to exercise and to induced anoxemia. Such studies, although subject to criticism, appeal to the clinician because they represent results obtained in man, not in animals, and results obtained from humans with coronary artery disease, not from animals with normal vessels. Riseman and Brown [6] determined the ability of different drugs to improve the exercise tolerance of patients with Heberden's angina who had been chosen after excluding those with financial, domestic, or social difficulties. The exercise duplicates the stimuli which usually precipitate attacks of ordinary activity. The number of trips over the two step apparatus required to induce a typical attack of angina pectoris was determined. Then each drug was administered for at least a week before evaluating the ability of the drug to increase the tolerance to exercise. The effect was estimated also clinically and subjectively, that is, the number of attacks after medication was determined and the patient was questioned as to his opinion of any improvement. By this method, nitroglycerin improved 60 per cent of the patients, quinidine sulfate about 40 per cent, codeine sulfate about 30 per cent, and atropine about 25 per cent. Over 30 per cent of the patients incurred untoward effects from aminophylline and atropine. An interesting result was the improvement of three of twenty patients given digitalis and on the other hand, the worsening of the angina in seven. This agrees with the usual opinion that digitalis is not beneficial. The degree of improvement in some patients was marked. Following the administration of nitroglycerin, five patients who without medication had pain after 35 trips were able to undertake as many as a hundred trips without pain. This effect lasted 30 to 60 minutes with 1/500 of a grain and longer with a dose of 1/100 of a grain. Gold [7] criticizes this work of Riseman and Brown because it does not take into account the spontaneous variations in exercise tolerance which occur in patients with coronary artery disease.

Levy and his co-workers [8] determined the efficacy of drugs in prolonging the time necessary for a 10 per cent oxygen, 90 per cent nitrogen gas mixture to produce anginal pain. They first determined the time necessary for the anoxemia to produce angina. They then gave the drug and the test was begun when the drug effect was known to be optimal. The time then quired to produce pain was determined and a four-ıead electrocardiogram was taken before and during the test. The sum of the R-ST deviations, in the four leads was contrasted before and after use of the drugs. This gave an objective index as to the drug effect. Aminophylline was given both intravenously, 8 mg. per kilogram weight, and by mouth four times daily for a week. Aminophylline and nitroglycerin were both effective as judged by subjective responses. Digitalis was given (1.5 Gm. total over four days) and on the fifth day by the anoxemia test the time of appearance of the pain was shortened by 9 per cent. This test, too, suggests that digitalis is a detriment rather than a benefit. Aminophylline intravenously increased the time necessary to produce anginal pain by 63 per cent. When given by mouth, it increased the time by 26 per cent. Nitroglycerin increased the time by 5 per cent. The ability of various drugs to prevent the deviation of the R-ST segment in the electrocardiogram and the degree to which the deviation was checked was considered objective evidence of the increased coronary blood flow.

The deviation of the R-ST segments in the controls added up to about 4.8 mm. Following both aminophylline and nitroglycerin, there was definite objective improvement, the sum of the deviations being only 2 mm. if the drug was given intravenously and a little over 3 mm. if given by mouth. An apparently slight improvement from lactose was not considered a significant change. The apparent improvement in coronary flow by this test following digitalis is not considered by Levy to be actual. He believes that because of the inherent digitalis effect upon the R-ST segment, this test is of questionable value for evaluating this drug. As the result of available data of the effect upon animals and man it is evident that aminophylline, nitroglycerin, and papaverine apparently are effective in improving coronary blood flow.

The ultimate evaluation of the efficacy of drugs must remain a clinical evaluation by the individual. The value of nitroglycerin for angina pectoris has been accepted by the practicing physician since its introduction by Murrell [9] in 1879. In effective dosage it has a low percentage of untoward effects. The other drugs advocated have not, as yet, withstood the test of time, nor have they fared so well in their early acceptance by many of the clinicians. There are active proponents and just as convinced dissenters regarding the use of the xanthines to promote increased coronary blood flow. The advantages have been given. The disadvantages are several. First, the uncertainty as to its efficacy in a dosage which has no toxic side-effects upon the patient. Second, the most popular of the group, aminophylline, has been shown by Starr and his collaborators [10] and by Boyer and Green [11] to produce stimulation of the heart in both man and dog. The

cardiac output and left ventricular work was increased and an adrenalin-like effect, though much milder, was induced. A further objection to answer if aminophylline is used, is the increased coagulability of the blood which Scherf and Schlachman [12] recently observed following the intravenous administration of 0.5 Gm. The coagulation time was shortened in 18 of 20 patients. This objection, too, must be balanced against its beneficial effects. Atropine and quinidine are not generally accepted for the treatment per se of angina pectoris. The undesirable effects usually outweigh their value. The clinician usually has felt that digitalis was a detriment rather than a benefit for primary angina pectoris. This is corroborated by the clinical and objective responses to the drug.

Possible Decholesterolizing Agents

Experience with lipotropic agents which mobilize lipids from the fatty liver has led to an attempt to affect coronary atherosclerosis by administration of low fat diet, thyroid, choline, and methionine. Herrmann [13] of Texas has reported on this work and feels it is promising. Its place in therapy has yet to be evaluated.

SPECIFIC TREATMENT OF THE VARIOUS CLINICAL TYPES OF CORONARY ATHEROSCLEROSIS

Latent Cases. The presence of a familial history of cardiovascular disease in a male over 40 certainly justifies a suspicion of coronary arterial disease. The employment of diagnostic aides may be justified to establish base line data for the future. The use of the response of the electrocardiogram to the exercise tolerance test of Master is certainly justified in a complete checkup. The anoxemia test of Levy is apparently no more accurate, has some hazards, and requires great care with rigid criteria for positive responses.

Angina Pectoris. One never knows in a patient with angina pectoris when coronary occlusion may occur, or we may more accurately say, when another coronary occlusion may occur. If attacks are more severe, more prolonged, or more frequent than usual we must consider the occurrence of coronary occlusion. If the pain remains transitory, one may employ a regime to prevent repeated attacks of transitory ischemia of the heart muscle. The treatment of angina must be based upon the idea that the longer an occlusion is delayed the more time anastomoses have to form. Since pain is the index of the ischemia and protracted ischemia is the cause of necrosis, sufficient restriction of activity to avoid pain is of paramount importance. This, plus the use of coronary vasodilators is essentially the medical treatment. The restriction of activity is by far the more important. The patient, we believe, will get little tangible benefit from vasodilators with the exception of nitroglycerin, employed not for relief of pain, but as a prophylactic of pain. Any activity or event which is regularly productive of anginal symptoms should be preceded by nitroglycerin. A short walk to the streetcar, ingestion of food, listening on the radio to a football game the patient will not forego, or any other such excitement, should be preceded by a dose of nitroglycerin. The avoidance of emotional tension, emphasized for decades, is still important. The addition of a possible 30 to 40 per cent increase in the heart load due to tachycardia and increased blood pressure is the reason. In regard to physical activity, it should be remembered that it is essentially the intensity of the activity which is detrimental and produces the disproportion between myocardial need and coronary supply. Many patients can perform slowly without pain the same act which if done rapidly, produces pain. Restriction of physical activity and emotional strain with the judicious use of nitroglycerin and the education of the patient in regard to the necessity of taking the drug as often as necessary is very important. Usually 1/200 grain chewed and held in the mouth will accomplish all that gr. 1/100 will, without the production of untoward side-effects. In some patients the administration at hourly intervals of 1/500 grain as advocated by Riseman, will give gratifying results.

There is a small group with such severe intractable pain that other measures are necessary. Surgical procedures are measures of last resort at present. The disagreeable after-effects of paravertebral alcohol injection together with the uncertainty of relief are reasons that lead to careful thought before undertaking such a procedure. Although many advocate its use, the few I have submitted to injection have not had benefit. On the other hand, I can recall instances when I advised it because of intractable pain. The patients refused and gradually improved so that they are now controlled by nitroglycerin and rest. Total thyroidectomy as a procedure has waxed and waned. Fauteux [14] has recently reported pericoronary neurectomy combined with ligation of the great coronary vein. He destroyed most of the nerve branches leaving or entering the left and right coronary arteries. He had operated on nine patients by ligation of the great coronary vein previously with good results. In dogs, this has been shown to hasten anastomotic circulation and to increase coronary blood flow. Whether this or other surgical procedures will survive the years, is uncertain.

TREATMENT OF MYOCARDIAL INFARCTION

It is difficult in many cases to differentiate between myocardial infarction or coronary occlusion without myocardial infarction. The clinician must depend upon the clinical picture to reflect the severity of involvement. When myocardial infarction or coronary occlusion is suspected, therefore, the treatment will depend upon the severity of the case as reflected in the clinical picture. The classification of Wood [15] of Philadelphia I believe is helpful. First, the severe case, a patient with severe prolonged pain, leukocytosis, shock, tachycardia, fever, and signs of cardiac insufficiency such as dyspnea, cyanosis, pulmonary edema, and basal râles. Second, the moderately severe case, one with pain, electrocardiographic signs of infarction, fever, and leukocytosis but no signs of cardiac insufficiency. Third, the mild case, a patient with pain, electrocardiographic changes, but no fever, no leukocytosis, and no signs of cardiac insufficiency. The fourth, the very mild case, one with brief pain lasting five to twenty minutes, but no other signs save that from this time on angina of effort will occur or if primarily present will be more easily produced. This probably represents occlusion without infarction and is due to an area with precarious blood supply which becomes ischemic only during exercise or emotion. The problem of bed rest in myocardial infarction is important. The amount of rest advisable is highly debateable at present. The clinician must choose a careful course avoiding the hazards of overactivity and the hazards of complete rest. The hazards of overactivity are the induction of sudden death, rupture, ventricular aneurysm, and the production of systemic emboli. Sudden death is unpredictable in coronary artery disease, but Dock [16] says that the Valsalva experiment as conducted with the patient at rest in bed is more productive of sudden death than allowing the patient out of bed. This not infrequently occurs when the patient is perched upon a bed pan and is an argument in favor of a commode at the side of the bed to be used in the less severe cases. It is not necessary to worry about the bowels for several days. Mineral oil is given from the start and the patient is carefully instructed not to strain. A liquid diet is preferable for the first few days, as patients do better on a semistarvation diet.

Rupture of the heart occurs in about 3 to 5 per cent of patients; usually it occurs early, in 98 per cent of them on or before the 16th day and is a little more prone to occur in those with hypertension.[17] Seventy per cent of them occur in people over 60 years of age. Absolute rest does not prevent rupture. Segall [18] says that the site of rupture is more important than the degree of the blood pressure. Jetter and White's [19] work showing a high percentage of rupture occurring in psychopathic patients, is evidence only of the effect of overactivity in the production of the rupture.

A third hazard of overactivity is ventricular aneurysm production. Sutton and Davis [20] in work on dogs found that if they exercised them vigorously there was no undue dilatation. This hardly applies to the treatment in humans as no one would exercise a patient with a myocardial infarct before six days.

The fourth hazard is the production of systemic embolism. It has been shown that the majority of patients with an infarct show ventricular thrombi and it could be expected that anything increasing ventricular contraction would tend to increase the number of emboli, therefore, activity could do it. Spain and Moses [21] in a recent study showed that 25 of 100 patients with myocardial infarcts had systemic emboli which contributed considerably to the death of the individual.

It is evident that for several weeks sudden physical strain should be avoided and the induction of the Valsalva experiment particularly. Emotional strain should be guarded against.

The hazards of complete rest have been emphasized greatly in the past few years, particularly those of thrombosis and emboli. Hunter [22] and others have shown that the majority of middle-aged people who are in bed for several weeks develop leg thrombi. One may ask how many patients with myocardial infarction develop pulmonary emboli from leg vein thrombi. In 100 necropsies, Spain and Moses found 36 with pulmonary emboli, 10 arising from the right ventricle, 14 from the right auricle, 10 from the leg veins, and two of undetermined origin. Therefore, it would appear that intracardiac thrombi occur in the majority of patients with myocardial infarction. Early treatment with dicumarol might possibly affect that favorably, but has not yet definitely been evaluated. In 61 instances of embolism in 100 cases, 36 pulmonary and 25 systemic, in only 10 instances were they from the leg veins. Therefore, contrary to the usual concepts we have had, if this study applies generally, apparently the hazards of intracardiac thrombi are greater than those resulting from leg thrombi. The other hazard of complete rest is that, with recumbency, edema of the lungs and hypostatic pneumonia more likely as are pulmonary infarction, or secondary myocardial infarction. However, it is not necessary to keep the patient recumbent and it is preferable for many to sit up in bed.

How much bed rest should we give the individual patient according to the clinical type? We agree with

Wood that the patient who has a severe attack, the one with severe prolonged pain, shock, tachycardia, fever, leukocytosis, and signs of cardiac insufficiency should have four to six weeks' bed rest. In general he should not be allowed out of bed for three weeks after the fever, leukocytosis, severe pain, and circulatory failure have disappeared. No walking is allowed until the sedimentation rate returns to the level before infarction, and the electrocardiogram has become stabilized. The interval for taking electrocardiograms ordinarily should be at the time of the attack and 48 hours later, then one a week for three weeks and then every two weeks until the pattern has become stabilized. Bed rest for the patient with a moderately severe attack; the patient with pain, electrocardiographic signs, fever, and leukocytosis but no signs of cardiac insufficiency, on the average, is three weeks. This is about two weeks after the fever, leukocytosis, and pain have subsided. Then the patient may sit in a chair. The interval before walking is allowed, is the same as that for the severe attack, that is, when the sedimentation rate has returned to the pre-attack level, and the electrocardiographic signs have become stabilized. For the patient with the mild attack pain and electrocardiographic changes, but no fever, no leukocytosis, no cardiac insufficiency signs, ordinarily bed rest from seven to ten days is adequate. Then he is allowed up in a chair and permitted to walk when the sedimentation rate is at the pre-attack level and the electrocardiographic pattern has stopped changing. The very mild attack, the one with very brief pain from 15 to 20 minutes but of a type which suggests coronary occlusion usually represents pain due to coronary occlusion without infarction. It often is precipitated by the introduction of some variable factors which suddenly either increase the demand or decrease the supply of coronary blood flow. A paroxysmal arrhythmia, unusual exertion, or excitement, by increasing the demand, or decreased coronary flow due to low blood pressure from shock or hemorrhage may produce temporary inadequacy. No infarction occurs and the coronary flow becomes adequate with correction of the precipitating factors. Activity must be restricted during that time.

TREATMENT OF INDIVIDUAL SYMPTOMS OF MYOCARDIAL INFARCTION

The control of pain is important. It has been our custom to use morphine sulfate intravenously at the beginning of the acute attack. Following that it may be given as necessary subcutaneously. One must avoid, however, the free use of morphine without concern as to the amount. Too often in the past we have given it too freely with production of such preventable bad effects as distention, vomiting, urinary retention, or respiratory depression which prove very annoying. Usually not more than 1 gr. is necessary in 24 hours.

TREATMENT OF SHOCK OCCURRING WITH MYOCARDIAL INFARCTION

The treatment of shock occurring with myocardial infarction is not easy to decide upon. The symptoms of pallor, cold extremities, sweating, weak pulse, low arterial pressure, diminished mental acuity, may or may not be due to the same mechanism as occurs in traumatic shock. The traumatic shock mechanism is that of diminished venous return, but frequently, if not usually, the shock occurring in myocardial infarction is that of cardiogenic shock, or, as Harrison says, hypokinetic forward failure shock which is due to a reduced output of the left ventricle, rather than fluid and protein loss through the capillary periphery as occurs in traumatic shock. The fundamental cause of traumatic shock is diminished venous return, but the shock of myocardial infarction may occur when there is an increased venous pressure such as occurs in congestive heart failure. Therefore, it is not a simple matter immediately to say that with shock plasma or fluid intravenously should be administered.

Gold,[7] in a recent discussion and conference on therapy in coronary artery disease, stated that for those patients whose skin is cold and clammy, the pulse is rapid, the blood pressure either so low or the pulse so feeble that the pressure cannot be registered by the ordinary methods, that plasma is indicated, that is, he accepts these findings as evidence of shock due to the mechanism similar to that of traumatic shock. He gives 250 cc. of plasma in the first hour and if the pressure comes up to 90 or 100 the injection is interrupted. The proper dose, he believes, is that which will fill the vessels sufficiently to raise the blood pressure to a safer level, usually about 100 mm. systolic. However, this is treating the shock of myocardial infarction upon an assumption. In the individual case it is very important to ask oneself what the mechanism is before treatment is started. If the blood volume is already normal or increased, congestive heart failure will be induced rapidly by administration of plasma or fluid. Until the decision is definitely made, it is advisable to treat the patient by oxygen and watchful waiting.[23] Extra fluid intravenously or glucose intravenously may do more harm than good.

The use of atropine and papaverine in a patient with myocardial infarction must be guided by the

individual reaction to the experimental work in animals. Undoubtedly when given to certain animals in large doses these drugs are beneficial by prevention of sudden death possibly due to reflex vasoconstriction, and by improvement of the coronary circulation and the production of smaller infarcts. However, the impossibility of giving drugs in the large doses which were necessary to prevent trouble in the dogs more or less raises a question as to the advisability of their use in relatively small doses in the human. It is not our practice to use any of them routinely.

The advisability of using dicumarol to prevent intracardiac thrombosis is not as yet settled. Certainly if intracardiac thrombi which occur in the vast majority of patients with myocardial infarction could be prevented it would prevent disastrous sequelae. However, at the present there are many objections to its use. First, the necessiay for daily laboratory work which is expensive. The daily venepunctures are annoying to the patient. Second, there is no certain evidence as to how long the dicumarol should be continued. Third, the hazards of dicumarol have not been precisely worked out. I do not believe yet that adequate data are available to show that there are not probably hidden dangers to the use of dicumarol. Certainly its routine administration at present should be discouraged. We have found the response to dicumarol quite unpredictable with, at times, abrupt disturbing changes in the clotting time. Work at present under way by the American Heart Association by which well-controlled studies are being made of the use of dicumarol should be ready in another year or so and the treatment then can be based upon accurate data.

The use of quinidine also is an individual matter. Its use routinely from the moment of the attack is advocated by some. In his recent edition, White [24] apparently feels its routine use is permissible. It must be remembered in the prophylactic use of quinidine, regardless of the condition which it is intended to prevent, that it probably protects the patient for only a few hours a day if given in three doses. The effect of quinidine is usually well dissipated in about four hours following its administration so that one must not be disappointed if arrhythmias arise despite its use. Personally we reserve quinidine for use in prevention of the ventricular arrhythmias if premature ventricular beats arise, or at the appearance of paroxysmal auricular flutter or fibrillation. In case auricular fibrillation or flutter develop we consider them as cardiac emergencies. Inasmuch as a large percentage of them persist and kill the patients, rather than spontaneously disappear, we believe that immediate treatment is indicated. Digitalis and quinidine are given immediately and continued until the termination of the auricular fibrillation or auricular flutter. The digitalis is given in the form of digitoxin (1.2 mg.) if the patient can take it orally. Quinidine is given 6 gr. every two hours until the arrhythmia is terminated. The development of paroxysmal ventricular tachycardia is serious and quinidine alone should be given inasmuch as digitalis tends to initiate and perpetuate the ventricular tachycardia. Again quinidine gr. 6 every two hours is given until termination of the arrhythmia. If the patient is nauseated or vomiting the preparation for parenteral use as devised by Sturnick [25] is used. This gives a concentration of 2½ gr. to the cc. and is quite effective. The use of digitalis alone in myocardial infarction is reserved for those patients with definite left and right congestive failure with regular rhythm. Based upon statistical studies, we believe that digitalis should always be combined with quinidine if auricular fibrillation is associated with the congestive failure.[26] Digitalis given alone without return of the arrhythmia to sinus rhythm apparently produces an increased number of systemic emboli.

There is an interesting complication of myocardial infarction or severe angina pectoris which may be misinterpreted if not thought of. A not infrequent development is that of a painful shoulder, painful to abduction or external rotation which may be erroneously ascribed to bursitis, periarthritis, or to pain from disuse.[27] This may be either in the right or left shoulder, may occur soon after, or several months after the attack, is often peculiarly made worse by heat, and responds to no particular treatment save time. A corollary of this is the frequent development of a stiff, swollen, painful hand with a smooth, glossy skin and often palmar erythema. This hand pain may develop with, after, or before the shoulder pain. Usually it follows the shoulder pain. It resembles arthritis but tends gradually over weeks and months to slowly improve. Later a Dupuytrens-like thickening of the palmar fascia may develop, usually, however, not developing the contracture of Dupuytrens, and often tending to abate a bit. This palmar thickening may develop slowly without the preceding acute signs of painful hand joints. Certainly it is found quite frequently in individuals with arteriosclerotic heart disease who presumably have had previous coronary occlusions. The syndrome is definitely ascribable to the heart, and the value of recognition lies in eliminating many therapeutic procedures that have been given for relief. There is little treatment save symptomatic relief and time. Irradiation of the shoulder may re-

lieve the shoulder pain. The swelling of the hand improves and is gone in an average of six months. There may be persistent stiffness for a year or so.

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The physician managing the patient having peptic ulcer must use several diagnostic tools and must be familiar with the varied therapeutic methods which may be applied. The practical application of these have been reviewed in this paper.

The Present Status of Diagnosis and Treatment in the Peptic Ulcer Problem*

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A concerted effort to establish the etiology, prevention and treatment for peptic ulcer has recently gained momentum. The disease is definitely on the increase. Each of the past two world wars has brought this fact to our attention more than ever before. When man power was urgently needed, we found that a comparatively large percentage of our population was incapacitated by peptic ulcers. One wonders if the cause for ulcers might not be an end-product of the patients' reactions to the lack of equilibrium in the social and economic status of society. Human beings are psychophysical animals—they think and do have emotional reactions which in turn seem to affect the internal organs.[1, 2]

ETIOLOGY

Focal infection, occlusion of gastroduodenal blood vessels, trauma in the epigastric region, gastritis, injury to the central nervous system, nervousness, gastric hyperacidity, gastric hypersecretion of pepsin [3] as well as free hydrochloric acid are but a few of the theories advanced as causative factors in the production of peptic ulcers.

Most certainly all of us have seen at various times patients in whom some of these factors are associated with peptic ulceration. Recently there was an opportunity of studying two children, five and twelve years of age, with gastro-intestinal complaints suggesting a clinical diagnosis of peptic ulcer. Each child presented physical signs, which when associated with the history, indicated that there had been same brain injury at birth. Roentgenologic study confirmed the clinical diagnosis of duodenal ulcer. A patient friend recently expired from a brain tumor. Four years before his death he had had a subtotal gastrectomy because of protracted syndromes due to pyloroduodenal ulceration. These illustrations do not imply that all of the previously mentioned theories are valid. Very few humans pass 20 years of age without acquiring some focal infection. Gastric analysis frequently reveals high amounts of free hydrochloric acid in normal people. In nervous patients high acid figures are very commonly observed. Nervous patients are so frequently met with in medical practice that, if they were all chronic peptic ulcer patients, the incidence on routine autopsies would certainly be higher than about ten per cent.[4] While acute ulceration is not uncommonly observed in gastritis, sufficient evidence has not been advanced to conclude that chronic peptic ulcers are caused by chronic gastritis. However, when these two conditions are associated the prognosis for permanent cure is less encouraging.[5]

Not infrequently one sees more than one peptic ulcer patient in the same family. This occurs too frequently to be a mere coincidence. The cause may be an inherited factor. However, as was observed during the war, ulcers seemed to develop more frequently in some unrelated individuals while under the same stress and strain.

It therefore seems logical to presume that the cause of this disease in a human being is a multiplicity of factors. These at present undetermined factors seem to result from the reactions of the organism to an environment that is physically and/or emotionally disturbing and intolerable to the particular person in question. The peptic ulcer patient or "candidate" for this disease has an unstable autonomic nervous system and, consequently, is different from many of his fellows.[6] He reacts more intensely to his environment.

As clinicians all of us have seen patients that did *not* have peptic ulcers but, nevertheless, had one or more of the aforementioned conditions suggested as causes in the production of ulcers. Further, all of us have seen patients with peptic ulceration associated with lesions of the central nervous system, chronic

* Lecture delivered May 2, 1947 under the auspices of the Graduate Education Committee of the Medical Society of the County of Queens under the title of "Recent Advances in the Diagnosis and Treatment of the Peptic Ulcer Patient."

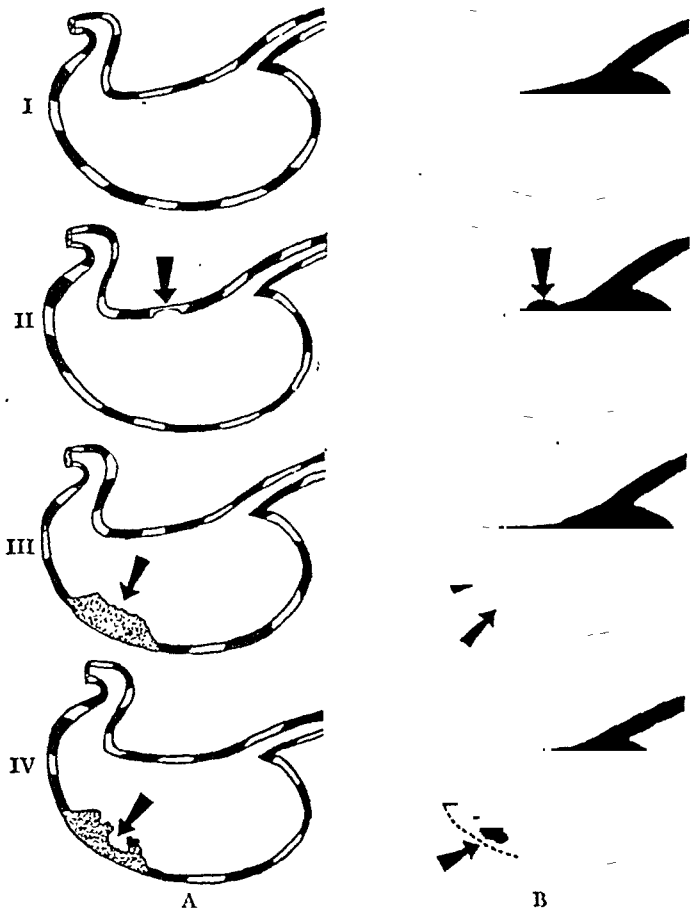


FIG. 1. Diagrammatic illustrations. Row A—View of stomach walls, lumen and lesions. Row B—X-ray visualization of lumen and lesion.

IA—Normal. Note lumen and thickness of gastric walls.

IB—Normal. A cast of the gastric lumen is formed by the ingestion of a barium solution. Only the shadow of the cast of the gastric lumen is visualized on x-ray study. The walls are not visualized.

IIA—Ulcer defect of lesser curvature of gastric wall. Ulcers at this site are practically always benign.

IIB—On x-ray plate the gastric lumen, which includes the lumen of the ulcerated area, is visualized. Note that the base of the benign ulcer defect is beyond the outline of the lumen.

IIIA—Neoplasm on the greater curvature encroaching on the gastric lumen. Neoplasms at this site are practically always malignant.

IIIB—On x-ray plate the gastric lumen is outlined and is visualized as narrowed and irregular where the neoplasm encroached upon it.

IVA—The neoplasm has become ulcerated. Note the defect into the neoplasm.

IVB—On x-ray plate the gastric lumen, which now includes the lumen of the ulcerated area, is visualized. Note that the base of the ulceration of the neoplasm is within the outline of the lumen.

gastritis, focal infection, etc. On the other hand, the author does not recall having seen a peptic ulcer "candidate" or patient that did not present unstable reaction to his environment. One must grant that the presence of gastric hyperacidity, focal infection, chronic gastritis, etc., could *in part* constitute the physically disturbing environment previously mentioned. Further, the continued presence of these states will influence the patients' general condition and act as deterrents in the healing of an existing peptic ulcer. Consequently, the treatment of a peptic ulcer patient must not only be directed toward the ulcer, but toward the patient as a whole. It seems that even when the ulcer-producing factors caused by the reactions of the human organism to his physically and/or emotionally disturbing environment are found and treatment to combat these factors is instituted, the patient will only benefit to the degree of relief or cure of the existing ulcer. The environment from a social, psychologic, physical and economic standpoint must be made tolerable to the particular patient in question, *and kept that way,* in order to prevent a recurrence.

DIAGNOSIS

Hunger-pain. The clinical diagnosis of peptic ulcer is largely dependent upon the symptom of hunger-pain. A didactic discussion of the other gastro-intestinal symptoms that also occur in other gastro-intestinal diseases as well as in peptic ulcer can be found in the average textbook on the subject. The hunger-pain syndrome, however, warrants some discussion and elaboration since it is the most constant and typical symptom of this disease. It is, however, important to bear in mind that the mere fact that a patient is hungry several hours after meals does not demand a diagnosis of peptic ulcer.

Hunger-like pain may be associated with eating insufficient bulk, chronic cholecystitis, chronic appendicitis,[7] early gastric neoplasm, hypoglycemia,[8,9] excessive use of tobacco, gastric hyperacidity, subtotal gastrectomy and gastrojejunostomy cases where the food quickly leaves the stomach.

Peptic ulcer hunger-pain is usually gnawing in character and is relieved by bland food or alkali. This symptom recurs periodically about one to two hours after meals with a tendency to present itself during the spring and fall of the year. Night recurrences are frequent if the patient has not taken some bland food or alkali before retiring. Although there are variations of the hunger-pain syndrome it is fairly safe to conclude that if the syndrome conforms to the aforementioned pattern, the diagnosis of peptic ulcer may be made even if one does not observe an ulcer niche on roentgenologic study.

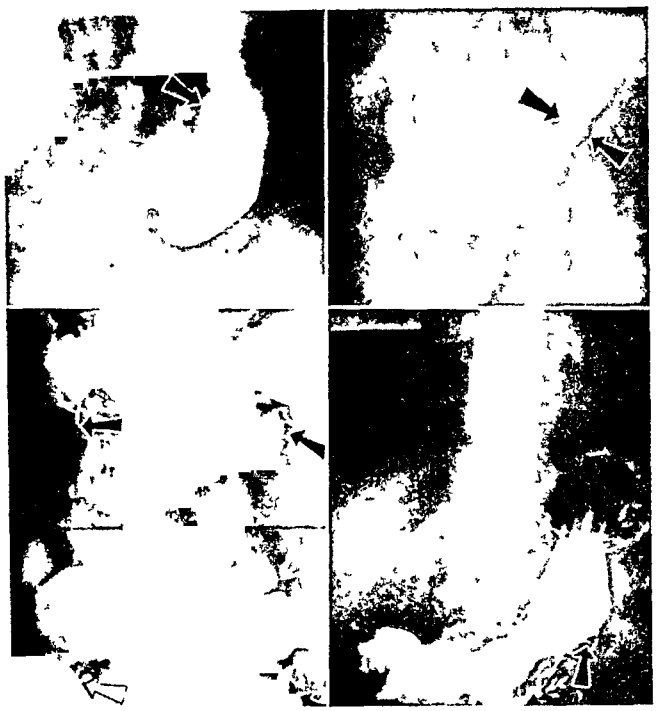


FIG. 2. (*Upper left*) A diagnosis of benign gastric ulcer had been made. Gastric analysis and gastroscopic examination had not been carried out. (*Upper right*) Same case, four months later. Gastric analysis revealed an anacidity, "coffee grounds" and thick mucus. Note the advanced filling defect. (*Lower left*) Ulcer defect of the third portion of the duodenum. (*Lower right*) Marginal ulcer. (Gastroscopically confirmed in the case where gastrojejunostomy has been performed.)

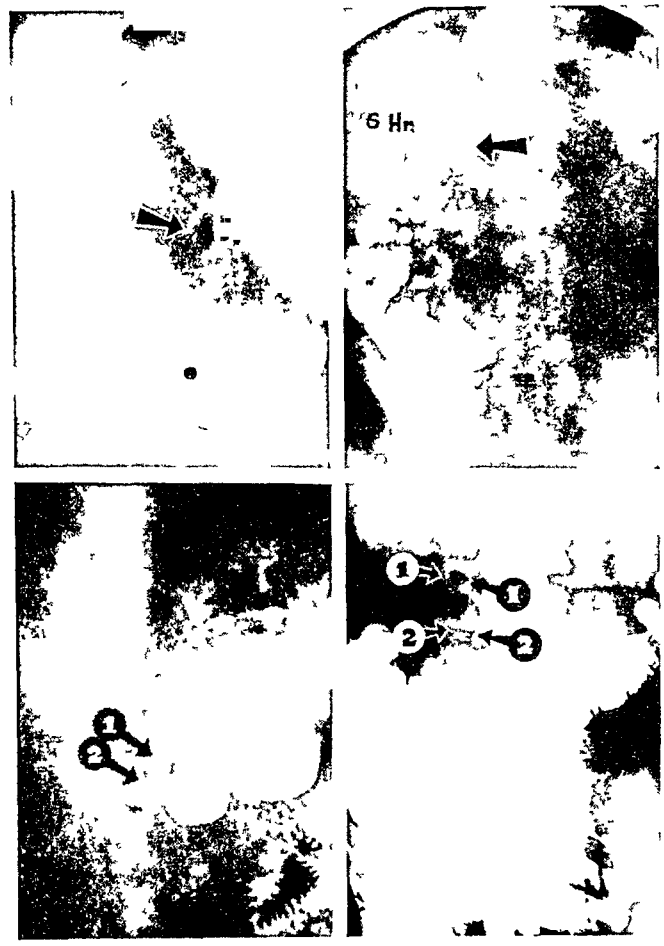


FIG. 3. (*Upper left*) Lesser curvature benign gastric ulcer perforated and walled-off (accessory pocket) in the space formed where the anterior and posterior gastric peritoneum unites to form the gastrohepatic ligament. (*Upper right*) Six-hour film presenting pathognomonic sign of ulcer. History was that of a peptic ulcer, but immediate films did not reveal an ulcer niche. (*Lower left*) (1) Accessory pocket formed by perforated duodenal cap ulcer. (2) Ulcer crater. (*Lower right*) (1) (Same case, six-hour study) Accessory pocket shown as gas bubble and faintly outlined by barium. (2) Pathognomonic sign of ulcer as evidenced by barium in the crater.

While reviewing[10] 102 unselected cases clinically diagnosed as having peptic ulcer, it was found that 29 did not have hunger-pain, but presented an ulcer niche on x-ray; 47 had both hunger-pain and x-ray evidence of ulcer; 26 patients had hunger-pain, but no ulcer niche was observed on gastro-intestinal x-ray study.

Physical Examination. On physical examination one may not observe any or many signs. In gastric ulcer patients I have usually been able to elicit tenderness on palpation at a point about one and one half inches to the left and above the umbilicus. In duodenal ulcer patients the tenderness is usually about one and one half inches to the right and above the umbilicus.

Gastric Analysis. Gastric analysis should be routinely carried out. The determination that there is free hydrochloric acid in the stomach is important since peptic ulcers are not found in achylia gastrica. This does not imply that a gastric carcinoma cannot degenerate and ulcerate in the absence of free hydrochloric acid. Low or absent free hydrochloric acid is indeed the usual finding in gastric carcinoma in contradistinction to peptic ulcer where the free hydrochloric acid figure is usually normal or high.

X-Ray Findings. (Fig. 1–4.) We often lose sight of the fact that x-ray films of the gastro-intestinal tract are not pictures of the organs under study. Actually, x-ray films are pictures of shadows of the opaque barium meal that is used to outline the gastro-intestinal tract. In other words, they are shadows of casts of the organs. It follows, therefore, that the thickness of the walls of, let us say, the stomach cannot be seen on x-ray. Only the lumen of the stomach is outlined. Hence, if a portion of the stomach wall is gouged out (ulcerated), the contrast media enters this area and outlines it in conjunction with the rest of the gastric lu-

men. The appearance is then that of a smooth niche which has its base *beyond* the outline of the lumen of the stomach. This is pathognomonic of benign ulceration.

On the other hand, if a neoplasm is present, the lumen is encroached upon. The barium outlines the lumen of the stomach. However, due to the encroachment of the growth into the gastric lumen, the outline usually presents a narrowed irregular appearance of a portion of the lumen. Should the neoplasm partly degenerate and a part be "gouged out," the narrowed

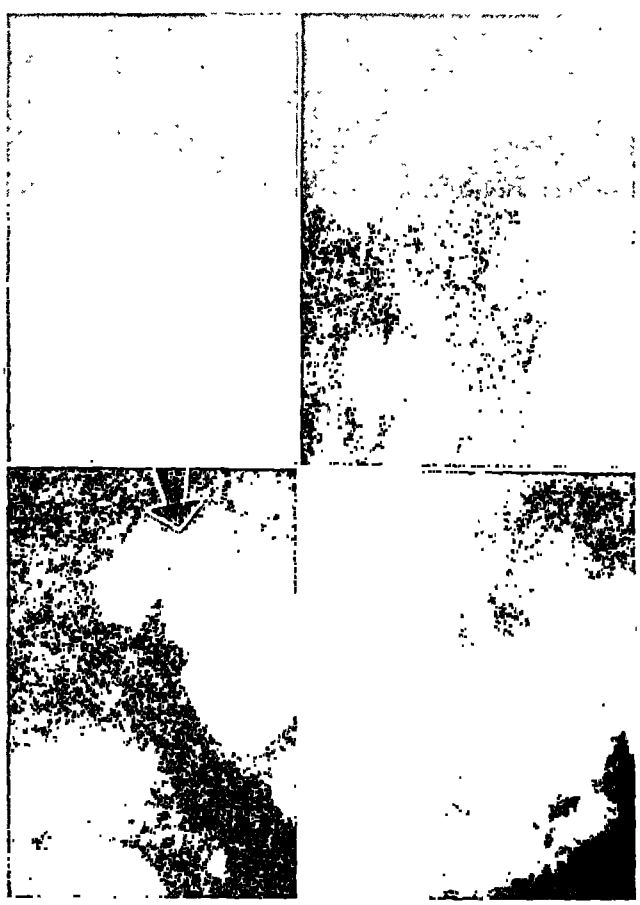


FIG. 4. Chronic duodenal cap ulcer defects. (*Upper left*) Clover-leaf deformity. (*Upper right*) Pine tree deformity. (*Lower left*) Plateau niche. (*Lower right*) Niche.

portion of the lumen would be outlined as having a niche. This is pathognomonic of ulceration of a neoplasm. This niche is usually not smooth; it has irregular edges. Its deepest part, the base, is *not* beyond the outline of the normal part of the stomach lumen.

Should an ulcerated area be shallow, it could not be visualized very readily. Further, if hemorrhage develops and a blood clot forms in the ulcerated area, as frequently occurs, the opaque barium meal cannot enter to outline the ulcer niche. The shallow and also the bleeding nonvisualized gastric ulcers can usually be seen on gastroscopic study. One hardly need mention that only about 50 per cent of hemorrhage from the gastro-intestinal tract is due to peptic ulcer.[11] Some other lesions that can cause hemorrhage are benign tumors, carcinoma, gastritis, duodenitis, polyps, esophageal varices, and blood dyscrasias.

Occasionally a peptic ulcer will perforate on the lesser curvature of the stomach into the small triangular area where the peritoneum covering the anterior and posterior gastric surfaces meet and continue on their path to form the gastrohepatic ligament. The base of the triangle is the lesser curvature. The perforation is walled off and an accessory pocket results. The contrast media will enter and outline this pocket thus establishing the diagnosis. Since only a localized peritonitis occurs in these cases, the patients usually do not present as dramatic a picture as patients with generalized peritonitis. They continue on into a stage of chronicity with the diagnosis being established, as a rule, long after the perforation occurred.

Duodenal cap ulcers are somewhat more difficult to visualize roentgenologically than gastric ulcers. The principle of the outlining of the lumen and niche of the duodenal cap is, of course, the same as that of the stomach. However, due to the size of the cap and thinness of its walls, the ulcer is shallower. Further, not infrequently, the duodenal cap may be behind the pylorus and thus be out of view. Studying the patient in the oblique positions and also with the duodenal cap under pressure will in most instances bring an existing ulcer niche into view.

An ulcer of the posterior wall of the duodenal cap is the most difficult to demonstrate by the very nature of its location. However, it is an important finding since that is the ulcer that is most apt to bleed. The pancreaticoduodenal artery is located just behind the cap. A sloughing of the ulcer with an erosion of that artery results in prolonged hemorrhage.

A duodenal cap ulcer niche may not be demonstrable on the x-ray films taken soon after the drinking of the barium meal. However, on the six-hour film one may see a speck of barium remaining in the region of the duodenal cap. When this finding is associated with a history of hunger-pain and/or irritability and tenderness over the duodenal cap on fluoroscopic study, it is reasonable to conclude that the speck of barium has remained in an ulcer niche. This is pathognomonic of a duodenal cap ulcer that may not have been visualized previously.

Deformity of the duodenal cap frequently results as the ulcer heals and the scar tissue thus formed contracts. These deformities roentgenologically may take

on the appearance of a clover-leaf, a niche or crater and/or a pinetree.

Gastroscopy. Gastroscopic study is an aid in the diagnosis of gastric lesions. Small gastric ulcers may be missed on roentgenologic study, if they are too shallow to be visualized or if hidden by overlying mucosal folds. The clinician may suspect but the roentgenologist may properly report that no ulcer was seen. Gastroscopy can usually clarify the situation. Marginal small submucosal hemorrhages surround the acute ulcer which is frequently multiple. They are probably the result of nutritional deficiency. Two acute ulcers involving the surrounding mucosa in a case of advanced gastric carcinoma were recently observed. Only the carcinoma was roentgenologically visualized.

Subacute ulcers are somewhat deeper with a muddy yellowish floor. The appearance of their surrounding mucosa is within normal limits. On the other hand, the mucosa around chronic ulceration takes on the appearance of gastritis. "The benign chronic ulcer has a definite line of demarcation with sharp overhanging edges and a white to yellow floor. The malignant ulcer is raised above the mucosal level. Its base tends to be from brown to almost black in color and the margins are irregular so that the immediate surrounding mucosa appears infiltrated. Errors in interpretation can be made, but if frequently repeated gastroscopy does not show healing, it is best to consider the ulcer malignant. It is difficult, if not impossible, roentgenologically to differentiate between benign and malignant gastric ulceration. One hardly need say that surgery is indicated at once in all malignant ulcers.

Following gastroenterostomy a marginal ulcer may be suspected because of persistent systoms. Due to puckering of the surrounding mucosal folds, a distorted x-ray picture may be observed. Through the gastroscope either an existing peristomal gastritis and/or the suspected ulcer could be found." [12]

TREATMENT

Anxiety for the cure of peptic ulceration is so great that revived, modified or new methods of treatment are frequently hailed as tantamount to cure for this disease. Unfortunately, to date many of the proposed treatments have been greatly overrated. As a cure none has survived the test of time. At present most of our treatments in uncomplicated ulcers are directed toward the relief of hyperacidity, hyperperistalsis and muscle spasm.

A detailed repetition of many of the older methods of peptic ulcer treatment will not be presented. Most of those methods are still basically sound. Nevertheless, it is fairly safe to repeat [13] that until the causes or cause of peptic ulcer are established, the treatment, with slight exceptions, will oscillate between those of today and those of yesteryear.

Except for the presence of some types of complication, the treatment of peptic ulcer is a medical, not a surgical procedure.

What appears to be benign obstruction at the pylorus does not indicate that surgery must be instituted. The obstruction may be due to an edema of the mucosa and not to scar contraction of a healed ulcer. In that event, gastric lavage, using about one quart of warm 2 per cent sodium bicarbonate solution several times daily has frequently resulted in a subsidence of the edema and relief from the obstruction. However, where the interference is due to actual scar tissue contraction, usually at the pyloroduodenal juncture, surgical intervention must be resorted to for relief from the obstruction.

Evidence that a gastric ulcer is penetrating is not necessarily an indication for resection. Most benign penetrating ulcers recede and tend to heal in three to six weeks of medical treatment with bed rest. The continuous alkaline drip is not necessary. The continuous presence of a rubber tube inserted into the stomach has proved both psychologically and physically disturbing to the patient. The results do not seem to be any better over frequent medication by mouth. If the penetration does not become smaller from the x-ray standpoint, the ulcer had best be considered malignant and surgical measures instituted.

The incidence of perforation of peptic ulcer seems to be increasing in females.[14] This complication is usually accepted as an indication for surgical intervention in both acute perforation and cases of slow leaks. The latter, which are usually not clinically recognized, lead to a walling-off of the lesion and the subsequent formation of the previously mentioned accessory pockets. It has been reported [15] that, if the stomach is promptly aspirated and kept empty by repeated aspiration, a perforated peptic ulcer will heal spontaneously.

Bleeding from peptic ulcers is rarely an indication for surgery. However, a surgical opinion should be sought early in every case of massive hemorrhage. The following was reported [16] as criteria when surgery is indicated.

1. Massive hemorrhage occurring in a known peptic ulcer patient over fifty years of age.
2. Massive hemorrhage occurring in a known peptic ulcer of long standing which has failed to respond to careful continuous medical treatment.
3. Massive hemorrhage following one or more previous episodes of severe bleeding from a peptic ulcer.

4. Massive hemorrhage from a known ulcer of long standing or in an arteriosclerotic patient failing to respond to one or two transfusions and there is evidence of continuous or repeated bleeding.

A suggested routine for medical treatment of bleeding peptic ulcers was reported some years ago.[13] Since it is still valid it bears repetition:

1. The treatment of the shock should be directed towards maintaining normal body temperature and mental and physical rest.

2. Continuous drip transfusion until all signs of active bleeding have ceased.

3. Early surgical consultation and treatment if it has been determined that surgical treatment is indicated.

4. Dietary routine as outlined by Andresen seems to conform better to the physiologic processes present.

5. Colloidal aluminum hydroxide, half a fluid ounce by mouth between feedings.

6. Vitamin C, 500 mg. daily during bed rest period; then gradually reduce the dose to about 300 mg. daily for perhaps six months.

7. Gastric lavage only in the presence of gastric distention associated with severe vomiting.

8. Unless the patient is much distressed, it is best not to treat constipation. If necessary, use a low saline enema or mineral oil by mouth.

9. Further investigations and treatment directed to focal infections, allergic conditions and roentgenologic study should be reserved for about three weeks after hemorrhage has ceased.

10. Bed rest for at least four weeks.

After care should be directed toward the treatment of the ulcer, e.g., easily digestible low-residue diet, antacid, sedatives and antispasmodics when indicated, no smoking or alcoholic beverages, at least eight hours sleep nightly, and avoidance of strenuous mental and physical exertions. Roentgenologic study every three to six months should be encouraged.

In severe gastric hemorrhage which is clinically and gastroscopically proved to be hereditary telangiectasia, it has been suggested [17, 18] that rutin in 40 mg. tablets be given thrice daily for from two to sixteen months. This medicament decreases the capillary fragility.

It has been demonstrated [19] that a duodenal ulcer patient requiring a gastrojejunostomy will tend to develop a marginal ulcer if the pre-operative gastric free hydrochloric acid figures were high. The subtotal gastrectomy procedure was used to prevent marginal ulcers. When the antrum and distal half of the stomach are resected together with the duodenal cap, the pepsin and a major portion of the acid-bearing glands are removed. In most of these patients an achlorhydria results. Thereafter, marginal ulceration rarely develops.

Subtotal gastrectomy is quite a mutilating operation. It has been recommended by me for peptic ulcer patients with accessory pocket formation and also in the presence of pyloric obstruction due to scar tissue when it is associated with hyperchlorhydria.

Regardless of the time of day most peptic ulcer patients have gastric hypersecretion, hyperchlorhydria, spasms and hyperperistalsis. The hypersecretion and hyperchlorhydria also develop when the stomach is empty. The cause for this abnormal secretion is problematic. It has been inferred that it might be due to a constant formation of some histamine-like products in the body [20-22] and/or to the continuous over-activity of the gastric secretory fibers in the vagus nerves.[23] Vagotomy is based upon the latter assumption as well as that of gastric hypermotility. Both are apparently favorably influenced [23-32] so that fasting acidity and hypermotility are usually markedly decreased. The reports [23-32] state that there is freedom from pain, x-ray evidence of healing of ulcers and practically no recurrences to date.

The favorable reports are phenomenal but are too recent for the drawing of final conclusions. Vagotomy is by no means a new method in the treatment of peptic ulcers. The first reference to vagotomy appeared in 1814.[33] In 1938 vagotomy with partial gastrectomy was recommended [19] for duodenal ulcer. In recent years Dr. L. R. Dragstedt and his co-workers have been principally instrumental in the research conducted with vagotomy. Bilateral vagotomy using the transthoracic approach for supradiaphragmatic severance of the vagus nerves seems to be the method of choice [34] at the present time. However, in about 90 per cent of cases the transabdominal subdiaphragmatic approach will permit almost an equally complete division of the gastric nerves.[33]

Vagotomy is not without its untoward effects. Fatalities can be expected and have been reported.[35] In a fair percentage of cases no achlorhydria results and occasionally there is no reduction in the gastric acidity although invariably the amount of night gastric secretion is reduced.[36] X-ray evidence of six- and even 24-hour gastric retention has occurred. Relief from this complication has been reported [37] by the use of urethane of B-methyl choline. Abdominal distention is a disturbing complication in many cases. Gastric motility apparently returns to normal several months after vagotomy and abdominal distention subsides. A mild diarrhea developed for a short period of time in about 40 per cent of a series of vagotomized patients.[32] Gastric acidity as well as gastric motility returns to normal

in about one year following vagotomy.[31] Therefore, there is reason to believe that the relief from pain which continues beyond the return of normal gastric acidity and motility, is due to the inability of impulses resulting from unpleasant environments to pass from the brain to the stomach after vagotomy. It has long been known that peptic ulcer patients, who have not had vagotomy, will develop exacerbations of their ailment when emotionally disturbed.

There is always the possibility of the severed vagus nerves uniting in the same manner as phrenic nerve endings grow together after phrenicotomy. In anticipation of this occurrence, the operation recommended [31] is vagus resection at which time a section of both vagus nerves is removed. This should minimize the eventuality of union between the nerve endings.

After vagotomy patients do give a gastric acidity response to histamine, alcohol and histamine-like substances that may be formed in the body in excess. Therefore, while this operation is a worthy contribution to the armamentarium for peptic ulcer treatment, it must not be regarded as a treatment to the exclusion of all other methods or adjuncts. One may dare speculate that, since the cause for peptic ulcer is a multiplicity of factors, vagotomy will prove to be but one adjunct in the treatment and will, as all single treatments, meet with its share of failures and recurrences of ulceration.

In the light of present knowledge and from all indications for the future the internist and/or gastroenterologist, not the surgeon, belongs at the helm for directing the treatment of the peptic ulcer patient. The co-ordination of consultants' opinions belongs in his hands. This does not imply that the "medical man" is possessed with the answer for the treatment; but it must be reiterated that, except for some types of complications, the treatment is a medical, not a surgical, procedure.

Sippy's routine of treatment was formulated with the intention of neutralizing the free hydrochloric acid and, thereby, to inactivate the pepsin. The major part of present day treatment is still directed towards that end. The two powders recommended by Sippy [4] were usually administered on alternating hours. These consisted of (a) two grams each of sodium bicarbonate and calcium carbonate, and (b) equal parts (0.65 Gm.) of heavy magnesium oxide and sodium bicarbonate. Prolonged use of the powders could cause an alkalosis. Further, they have an unphysiologic alkalinization effect on the gastric contents, with a resultant secondary gastric hypersecretion. During the course of a research problem with protein hydrolysate, it was demonstrated that the amino acid mixtures likewise have a secondary secretagogue effect.[38]

In recent years aluminum hydroxide gel preparations have replaced the alkalinizing agents previously used. These have the advantage of not having any secondary secretagogue effect. Further, since these preparations are not absorbed, there is no disturbance in the systemic acid-base balance and no alkalosis develops.

Unfortunately, most of the aluminum hydroxide gel preparations are constipating. To avoid this disturbing effect, an equal amount of magnesium trisilicate is added to the preparations of aluminum hydroxide gel. Since proper bowel activity is important, the choice of preparation must be guarded. There are two types of alumina gels—reactive and nonreactive. The reactive variety has much the same chemical effect on the gastric acid as, for example, silver nitrate has on hydrochloric acid. In contradistinction, the nonreactive aluminum hydroxide gel does not seem to have any chemical effect on the gastric acid. It seems, so to speak, to take away the acid's freedom of action. The offending gastric acid becomes a prisoner of the nonreactive aluminum hydroxide gel.

At the end of a comparative clinical research study [39] the following conclusions were reached:

1. Reactive aluminum hydroxide gel with an addition of magnesium trisilicate is constipating.
2. Nonreactive aluminum hydroxide gel without an addition of magnesium trisilicate is less constipating than the first preparation.
3. Nonreactive aluminum hydroxide gel with an addition of magnesium trisilicate is not constipating; it promotes bowel activity.

It has been suggested that a combination of colloidal aluminum hydroxide gel and magnesium hydroxide acts for several hours in the stomach as a stable buffer, does not become a secretagogue, does not have a systemic alkalosis effect and is not constipating.[40] This author has not had any experience with that combination, but the aforementioned study has given similar results with the combination cited above under item (3).

An antispasmodic and sedative mixture is usually advisable before, after and midway between meals as well as before retiring. The choice of the medicaments may be atropine and phenobarbital or any of the derivatives or combinations that are generally accepted as effective. Since peptic ulcer patients experience symptoms, treatment should be in anticipation of the symptoms rather than waiting for their appearance.

Studies carried out[41] between 1930–1934 revealed that extracts obtained from intestinal mucosa contained a humoral agent that inhibited gastric motility and secretion. The early workers, Ling, Liu, Kosaka and Lim suggested that this agent be named enterogastrone. In 1937, Gray, Bradley and Ivy[42] purified and assayed enterogastrone. Whereas vagotomy abolished the tract for nerve impulses from the brain to the stomach that would otherwise cause gastric hypersecretion and hypermotility, enterogastrone "given parenterally inhibits or abolishes the gastric secretory response to histamine."[22] This humoral agent is produced if there are sufficient concentrations of sugar and fat in the chyme. One wonders if peptic ulcer patients would be favorably affected by the introduction of high concentrations of sugar and fat directly into the small intestines. Not the least of the contributions of enterogastrone is its prolonged inhibitory effect on gastric secretion. This effect has lasted as long as 27 months, after discontinuing treatment with the medicament.[22]

The indirect part that histamine plays in the production of peptic ulcers is in direct proportion to the influence that histamine-produced hyperchlorhydria exerts in the production of ulcers. To date there has been an unsuccessful clinical effort to combat with antihistamine drugs the effects of histamine-produced hyperchlorhydria. Perhaps enterogastrone will be the answer. An enterogastrone-like substance, urogastrone, has been extracted from the urine of pregnant women.[21, 43]

Antihistamine qualities are present in the amino acids, histidine, cysteine and arginine.[44] However, effective doses of arginine would prove fatal. Since these amino acids are members of the basic constituents of protein hydrolysate, the antacid quality of that hydrolysate may in a small measure be due to the slight antihistamine effect of the aforementioned amino acids.

Experimentally, Benadryl does have an antihistamine effect in diminishing gastric histamine-produced hyperchlorhydria.[20] For practical clinical purposes it has no appreciable value in the treatment of the gastric hyperacidity of peptic ulcer patients. To date, the same seems to apply to the other commercially recommended antihistamine drugs. One concern manufacturing an antihistamine product recommends a course of 21 daily injections. With experimental use, no clinical improvement that could be credited beyond all doubt to that drug has been observed. Conventional methods of treatment have given similar results in periods of three weeks or less. In cases of known allergic states, associated with an ulcer, it seems desirable at times to recommend ten units of histaminase half an hour before the three main meals during the allergic period.

Protein-rich diets have been used by some from time to time in the treatment of peptic ulcers. However, the usually prescribed diet for this malady is more often than not low in protein. Consequently, hypoproteinemia is not infrequently associated with prolonged chronic peptic ulceration. Protein hydrolysate, which consists of amino acid mixtures, has been recommended[39, 45-56] and proved to be an effective combatant for hypoproteinemia. Amino acid mixtures have antacid qualities. Co Tui and his associates,[45] therefore, correctly reasoned that beneficial results should develop from the use of protein hydrolysate in chronic peptic ulcer cases. Their reasoning was confirmed when protein hydrolysate treatment was started. Clinically, the improvement was striking. Hunger-pain disappeared or decreased almost immediately. The minimizing or disappearance of belching, heart-burn, nausea and vomiting soon followed. In some instances heart-burn and/or diarrhea developed, but subsided as a rule in four to five days if treatment was continued. The patients gained weight and seemed to have a feeling of well-being. X-ray evidence seemed to suggest healing of the ulcer. Further confirmation by repeat x-ray studies and gastroscopic examinations is necessary. X-ray evidence of improvement may be due to subsidence of an associated duodenitis and/or gastritis.

A series of ambulatory chronic peptic ulcer patients were in the process of similar treatment and observation.[57] It had been noticed that the clinical course was strikingly similar to Co Tui's group of patients. However, many of the patients had a return of hunger-pain about as frequently as recurrences develop with older methods of treatment.

The dose is one ounce (approximately four tablespoonfuls) of protein hydrolysate daily for each 50 pounds of body weight. The total is divided into equal doses of 45 Gm. and each one is mixed with 45 Gm. of Karo syrup in one-half cup of milk, fruit juice or broth. The total number of doses is divided into the average waking hours (16 hours), the resultant figure being the interval in hours between each dose. This procedure is followed for two weeks. At the end of that time, the Karo syrup is omitted and only two tablespoonfuls of protein hydrolysate in one-half cup of any of the aforementioned liquid carriers is taken about one hour after each of the three main meals and an hour before retiring for the night.

It has been experimentally demonstrated [38] that protein hydrolysate in 45 Gm. doses presents its best antacid effect. This effect is obtained at one hour after ingestion of the medicament. However, regardless of the size of the dose, up to 50 Gm., protein hydrolysate becomes a gastric secretagogue at the end of one and one half hours, at which time a hyperchlorhydria develops. Therefore, a supplementary antacid, like a nonreactive aluminum hydroxide gel preparation, in an average dose of two teaspoonsful is recommended one hour after taking protein hydrolysate.

The advantage of this combined routine over the conventional antacid therapy is the giving of an antacid and an easily absorbed food to combat hypoproteinemia. The resultant feeling of well-being is superior to that obtained by any of the older methods. The gain in weight is an advantage in the event of complications.

The disadvantages are the high cost, the bulk and cumbersomeness of preparation, the unpleasant odor and taste of protein hydrolysate. The components of protein hydrolysate are such that if the taste and odor are to be favorably altered, it must be at the expense of some of the essential parts of the amino acid mixture.

Dietary regimes can easily be arranged. Various modifications of a bland low-roughage, high-protein, high mixed-vitamin and mineral-salt diet is the diet of choice. A good rule to follow is the greater the disturbing symptoms the more frequently small feedings should be employed, and the diet should then be liquid or semisolid.

From time to time controversies develop as to the advisability of feeding bleeding peptic ulcer patients.[58-61] The Andresen [60] regime seems to be most suitable. The Meulengracht [61] regime seems to be excessive in the presence of bleeding.

We are often asked how long it takes for an ulcer to heal. In a study [62] of 63 duodenal ulcer craters it took an average of 40 days with a range of 13 to 230 days. The time was measured from the date of first x-ray visualization to its subsequent nonvisualization. Obviously, this is inaccurate since asymptomatic ulcers may exist for a period of time before x-ray study becomes indicated by onset of symptoms. Further, as ulcers heal they become smaller and shallower. We know that small and shallow duodenal ulcers may not be visualized on roentgenologic study. The healing time undoubtedly varies according to the site of the ulcer, environment and treatment. An asymptomatic and roentgenologically inactive ulcer may be considered as healed.

SUMMARY

Obviously only the most pertinent phases in the diagnosis and treatment of peptic ulcer have been presented.

The following important diagnostic factors have been discussed in detail:

1. Periodic rhythmical hunger-pain relieved by food and alkali is the most important reliable symptom.

2. Not infrequently, tenderness is elicited on palpation at a point one and one half inches to the right and above the umbilicus in cases of duodenal ulcer. In gastric ulcer cases the tenderness is the same distance above and to the left.

3. Peptic ulcer does not develop if there is no acid in the gastric secretions. In peptic ulcer cases gastric analysis reveals normal or increased acid figures.

4. The usual finding on x-ray is a niche defect of the stomach or duodenum.

5. Gastroscopic examination may bring shallow gastric ulcers into view. These ulcers usually are not observed on roentgenologic study.

Treatment was subdivided and discussed as:

A. Surgical

1. Marked obstruction due to scar contraction.

2. Subtotal gastrectomy in the presence of an accessory pocket and/or pyloric obstruction due to scar contraction when associated with hyperchlorhydria.

3. Vagotomy for the purpose of eliminating the pathways to the stomach for impulses arising in the brain that were stimulated by offending environmental conditions. Vagotomy eliminates that phase of gastric hypermotility and hyperacidity.

B. Medical

1. The internist and/or gastroenterologist should always be at the helm in directing the treatment. Peptic ulcer is primarily a medical, not surgical, disease.

2. Nonreactive aluminum hydroxide gel is the antacid of choice.

3. Enterogastrone seems to be an effective antihistamine for depressing the histamine phase of gastric hyperacidity and hypermotility. Other antihistamine drugs have not proved their effectiveness toward that end.

4. Protein hydrolysate is effective in abating symptoms and eliminating hypoproteinemia when associated with chronic peptic ulcer. Its antacid effect ceases at the end of one hour and it then has a secretagogue action. This medicament should, therefore, be supplemented at the end of one hour by a nonreactive aluminum hydroxide gel.

5. The greater the disturbing symptoms the more frequently small liquid or semisolid feedings should

be employed. For ambulatory cases a bland, low-roughage, high-protein and high-vitamin diet is indicated. In peptic ulcer hemorrhage, the Andresen regime for feeding is recommended.

CONCLUSIONS

The problem of peptic ulcer is more than just limited to the lower esophagus, stomach and small intestines. The peptic ulcer patient must not only be considered as an organism that is afflicted, he must also be studied from the viewpoint of the human being that he was and is. In addition, the emotional reactions of the patient and his family to the past and present environment must be investigated—for we are not only what we are today, we are also all that has preceded us. It is these ramifications that make the treatment of the peptic ulcer patient so intriguingly complicated. A peptic ulcer is a local manifestation of a systemic disease resulting from the reactions of the patient to an environment that is physically and/or emotionally disturbing and intolerable to him. It has been attempted to illustrate that, as we recognize these facts, we approach the goal for more scientific and better social treatment of this disease. We do not have the final answer for the cure, but we are making headway.

Should we become discouraged for even a single moment, we must never forget that we are learning and that

> Knowledge acquired today
> May seem as not a gain;
> But as the years roll by
> Its wealth we shall attain.

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A concise presentation of the action and uses of diuretics in the treatment of edema.

Principles in the Use of Diuretics*

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Cardiac edema is generally conceded to be associated with retention of salt and water. The "backward failure" proponents believe that the fluid is forced into the tissues by a high venous pressure. The "forward failure" concept seems to be receiving increasing support. Experimental evidence for this is presented elsewhere [1-3] but briefly it consists of the following. When the cardiac output becomes inadequate for tissue demands the efferent arterioles of the kidney contract in response to an unknown stimulus to divert blood to tissues whose metabolic needs are greater than those of the kidney. The efferent arteriolar constriction produces a rise in filtration pressure, which maintains a relatively normal filtration rate until the renal plasma flow falls below 200 cc. per minute. Below this point the filtration rate falls rather rapidly. Thus the filtration of salt and water is greatly reduced whereas reabsorption continues to be almost complete which results in a retention of salt and water with edema formation. This retention seems to occur in resting cardiac subjects at filtration rates of below 70 cc. per minute. This concept seems to explain more adequately than the backward failure theory the great importance of salt restriction in the edematous cardiac patient.

Diuretics, in order to reduce edema, must cause increased elimination of sodium as well as water. Schemm [4] and Wolff [5] contend that water when given with a limited salt intake will itself produce a sodium diuresis. Studies in our laboratories [6] and work by Crutchfield [7] do not bear this out. Further work is being done to attempt to account for these discrepancies.

Diuretics are indicated in congestive heart failure when, despite the use of digitalis, limited activity and limited salt intake, the patient has (1) attacks of paroxysmal nocturnal dyspnea, (2) dyspnea on moderate exertion, (3) enlargement of the liver due to congestion, or (4) distended neck veins. One does not wait until pitting edema is evident, for the patient may accumulate as much as 15 pounds of excess fluid before clinical edema appears. After dehydration of the patient to the condition of maximum comfort his weight should be determined. A gain above this basic weight of more than three pounds of fluid is usually an indication for administering another dose of the diuretic.

The chief contraindications to the use of diuretics are renal insufficiency and acute glomerulonephritis. Large amounts (3 to 4 plus) of albumin are often seen in heart failure and do not preclude the use of these drugs. A moderate elevation of the blood NPN to as high as 70 to 80 mg. per cent may be seen in uncomplicated severe heart failure due to reduced filtration by the kidneys. Levels above this demand extreme caution in the use of mercurials, acid-forming salts, potassium salts, and urea. A normal PSP test does not always mean that these substances may be given with impunity since the PSP test depends on the function of the proximal convoluted tubules while nonprotein nitrogen excretion is related to filtration. In patients with thickening of Bowman's capsule caused by glomerulonephritis, filtration may be greatly reduced in the presence of a normal PSP test. The inulin clearance is the most accurate index of such a state but is not practical for clinical use. The urea clearance test is quite satisfactory, but for practical purposes severe limitation of filtration is indicated by an elevation of a single blood NPN or urea level.

Acid salts are useful particularly in patients with mild edema because alone they may suffice to control the edema. The exact mechanism of their action is uncertain. Some believe that the acidifying action causes water shifts which favor elimination; [8] others think that the function of the kidneys in maintaining acid-base equilibrium causes the renal tubules to reject the excess anions which carry fixed base and water with them into the urine. Ammonium chloride is one of those most commonly employed. The ammonia radical forms urea leaving the chloride ion free to carry away sodium. It is given to the point of gastric tolerance, usually about 4 to 6 Gm. daily, either

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continuously or with intermissions of two to three days weekly to avoid gastric irritation. It is also given prior to injections of mercurial diuretics, as the diuresis from the two combined is greater than a simple additive one from each alone.[9]

Osmotic diuretics act by simply carrying off an obligatory amount of water with them, and since they increase sodium excretion relatively little they are not extremely effective. Fifty per cent glucose intravenously may be used when more active diuretics are contraindicated. Sucrose seems to be toxic to the convoluted tubules and is no longer used.[10] Urea is quite useful in patients with moderate failure and relatively good renal filtration. It is given orally in grapejuice in doses of 30 Gm. three times a day. Its disagreeable taste prevents a wider usage.

The xanthine group acts by decreasing reabsorption of salt and water by the tubules.[11] Theophylline is by far the most potent and is the best of oral diuretics with the possible exception of mercurials, but unfortunately it causes marked gastric irritation and can rarely be given for more than two or three successive days. Its salt aminophylline is not very effective. It may be alternated with an acidifying salt. Doses of 0.3 to 0.6 Gm. three times a day may be given. Theobromine is less active but is better tolerated and may be given in larger doses of 0.6 Gm. three to five times a day. Caffein is not a very potent diuretic. The salts of this group containing sodium would seem to defeat their own purpose since it is sodium that we are trying to eliminate.

Mercurial diuretics have added many years of comfort to lives of thousands of cardiacs. They are by far the most potent of diuretics. While some evidence has been presented to indicate that they cause a release of bound water and produce a diuresis in this way, the overwhelming weight of evidence shows that their primary action is to decrease reabsorption of salt and water by the proximal convoluted tubules.[12-14] Normally about 99 per cent of the filtered salt and water is reabsorbed by the tubules. If only 98 per cent is reabsorbed the urine output will be doubled. Thus only a slight effect upon the tubules by the mercury is required for a good diuresis. The diuresis begins one to three hours after administration of the mercurial, reaches its peak at about six hours and is over in 12 to 24 hours. A slight increase in urine flow is evident in some patients during the second 24 hours. There seems to be little choice between the three commonly used mercurials, mercupurin, salyrgan with theophylline, and mercuhydrin. All contain theophylline which seems to help prevent sloughs if the material leaks into the tissues.[15] It also makes intramuscular administration less painful. Some evidence has been presented to show that mercuhydrin is less toxic than the other two but this is not striking. Some of the reactions are those of general mercury poisoning with diarrhea (sometimes bloody), abdominal cramps, etc. Muscular cramps occasionally occur, supposedly due to chloride deficiency, and may be prevented by simultaneously giving ammonium chloride. In rare cases sudden death has been reported presumably due to ventricular fibrillation.[16] Another serious reaction is a shock-like syndrome thought to be produced by sodium depletion. This is relieved by sodium chloride administration. In three instances the author has repeatedly seen a reaction to mercuhydrin which is apparently benign. The patient becomes acutely dyspneic and remains so for about three to five minutes. In one of these subjects the reaction has become less pronounced with subsequent injections and has almost disappeared. In the other two it was necessary to discontinue the drug. Salyrgan and mercupurin failed to produce the reaction in these same individuals. Reducing the rate of administration seemed to decrease the severity of the response. It does not occur with intramuscular use. Mercuhydrin seems to cause less pain by the intramuscular route than the other two, some patients complaining not at all, though some complain bitterly. Mercupurin suppositories, now called mercuxanthin, produce a very satisfactory diuresis though not as great as via the intramuscular and intravenous routes. Severe rectal irritation and pain occur in some subjects but others tolerate the suppositories quite well. Oral tablets of salyrgan with theophylline are available to be given five at a time about once or twice a week. The diuresis is not nearly so marked as that produced by other routes but some fluid is lost by the diarrhea which frequently occurs with the tablets. Many patients have some diarrhea and abdominal cramps.

The dosage of mercurial diuretics is 0.5 to 2.0 cc. and some have given as much as 3 cc. without untoward reaction. This may be repeated as often as twice a week indefinitely without giving any evidence of renal damage at autopsy. I have seen one patient who received 2 cc. daily for three weeks without evidence of renal irritation but this is not recommended. The frequency of administration is best guided by the patient's weight as outlined above. Mercurial diuretics may produce irreversible fatal uremia in patients with impaired kidney function, since a high concentration of mercury may become fixed in the tubules of the remaining active nephrons. No patient with malignant hypertension should receive these drugs without obtaining a blood NPN determination. No patient of

any type should receive a mercurial if the NPN is above 100 mg. per cent. Blood NPN concentrations of as high as 60 mg. per cent are not uncommon in heart failure but levels above this should make one proceed with great caution and with very small doses of mercurials, checking the NPN after each dose at first. Benign hypertension and marked albuminuria are no contraindications to the use of these drugs. Patients with the nephrotic syndrome of glomerulonephritis and patients with cirrhosis of the liver are sometimes benefitted by mercurial diuresis.

Digitalis is a diuretic when it raises the cardiac output. Slight rises in renal plasma flow secondary to the rise in cardiac output may greatly increase the filtration rate. Furthermore, the increase in urine output may be far out of proportion to the increase in filtration rate as a greater percentage of the filtrate seems to be rejected.[17] The most spectacular results occur with auricular fibrillation in which the cardiac output may be almost doubled.

With the use of diuretics the signs of congestive heart failure may disappear and the profound weakness associated with inadequate blood flow to the muscles may become pronounced because of the increased activity permitted by the relief from dyspnea. Diuretics aside from digitalis-like preparations do not seem to influence the cardiac output and do not prevent these symptoms.

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New Syndrome

The discovery of a new clinical phenomenon is a sufficiently rare event to be worth recording.

In the history of a patient newly admitted to a hospital I read that he had noticed that his urine had turned green. I observed to my house-physician that he had no doubt been taking backache pills containing methylene blue, but was informed that the patient had haematuria and was colour-blind.

——From *The Lancet,* November 1, 1947, p. 668.

The effectiveness of the antihistaminic drugs has been established in certain of the allergic skin diseases. Here the authors evaluate their worth as antipruritic agents in itching skin lesions not necessarily of allergic origin.

The Treatment of Itching Dermatoses with Antihistaminic Drugs

With Particular Reference to Pyribenzamine *

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Recently Feinberg [1] summarized most of the work with Benadryl and Pyribenzamine in the United States. These drugs have now been widely used in many allergic and some nonallergic diseases. Very early during the clinical investigation of the so-called antihistaminic drugs,† it was noted that they exert a significant effect not only on certain dermatologic lesions, but also on the important subjective sensation of *itching*. It was obvious that if they exerted a definite antipruritic effect in a significant proportion of cases the antihistaminic drugs would be valuable adjuvants in the treatment of itching dermatoses. A preliminary report by Baer and Sulzberger [2] dealt with an appraisal of Pyribenzamine in the treatment of itching dermatoses, and concluded that Pyribenzamine exerted a significant antipruritic effect in some cases.

Since then we have had the opportunity to study the effects of antihistaminic agents in several hundred patients with various allergic and nonallergic pruritic dermatoses. For various reasons approximately 80 per cent of cases were treated with Pyribenzamine and approximately 20 per cent with Benadryl.‡ While the present discussion in general deals with the effects of both Benadryl and Pyribenzamine, the data given in Table 1 are based exclusively on our experiences with Pyribenzamine.

THE EFFECT OF ANTIHISTAMINIC AGENTS ON CLINICAL DERMATOLOGIC LESIONS

A striking objective effect could be observed only in certain of the whealing lesions. This effect was of course most noticeable in urticaria, including urticarias due to physical agents (cold, light, stroking, etc.),[3] but was also seen in the urticarial elements of those dermatoses which present wheals in addition to other lesions (e.g., some cases of multiforme erythemas, dermatitis herpetiformis, acute eczematous contact-type dermatitis).

No such *direct* effect of the antihistaminic agents was noted on any of the many other types of dermatologic lesions.§ However, while there was no visible direct effect of the antihistaminic drugs on nonurticarial skin lesions, the indirect effects achieved were sometimes of clinical importance. In some cases such indirect effects were obviously achieved through a reduction of itching and the consequent reduction in scratching and other external traumatization.

THE EFFECT OF ANTIHISTAMINIC DRUGS ON ITCHING

Because of the purely subjective nature of itching the evaluation of the effects of antihistaminic drugs on this sensation was much more difficult than the appraisal of their effects on the clinical lesions. We employed the following criteria for estimating antipruritic effectiveness:

* We are indebted to the Ciba Pharmaceutical Co., Summit, N. J., for supplying us with a portion of the Pyribenzamine used in this study.

† The word "antihistaminic" is used throughout in order to comply with present usage. It does not signify the authors' opinion that the antihistaminic action of these drugs is necessarily their only or major mechanism through which they produce these effects.

‡ One of the reasons was that Pyribenzamine was placed at our disposal earlier than Benadryl.

§ This applies also to eczematous lesions, a fact of interest because R. L. Mayer [4] has recently reported on inhibitory influence of Pyribenzamine on the dermatitis resulting from deliberate experimental sensitization of guineapig skin with simple chemicals. This effect in the experimental animal occurred at a dosage level (amount per kilogram of weight) many times that used by us in human beings.

TABLE I

*Antipruritic Effects of Pyribenzamine in 124 Cases of Itching Dermatoses**

	Total Cases	Good to Excellent Relief from Pyribenzamine Alone	Fair Relief from Pyribenzamine Alone	Fair to Excellent Relief from Pyribenzamine Plus Other Treatment	No Relief	Insufficient Data for Evaluation
Urticaria, Acute	6	2		2	2	
Subacute	4		1	3		
Chronic	13	6	2	1	2	2
Physical	1		1			
Atopic Dermatitis	27	1		11	13	2
Eczematous Dermatitis with Urticarial Features	3	2		1		
Eczematous Dermatitis	23	1	1	7	9	5
Multiforme Erythemas	2			1	1	
Chronic Discoid and Lichenoid Dermatosis	3				3	
Acne Vulgaris	1				1	
Psoriasis	2		1		1	
Lichen Planus	2		1			1
Dermatitis Herpetiformis	2				2	
Exfoliative Erythroderma	1				1	
Lichen Chronicus Simplex	3	1		2		
Pruritus Vulvae	8	2		3	1	2
Pruritus Ani	3			2	1	
Pruritus Senilis	1				1	
Pruritus (postscabietic)	1			1		
Pruritus (unclassified)	8	2		2	3	1
Seborrheic Dermatitis	2			1	1	
Herpes Gestationis?	1					1
Dermatitis Medicamentosa	3			2		1
Cases for Diagnosis	4			1	3	
Totals	124	17	7	40	45	15

* In this table are included the 56 subjects reported on previously.[2]

1. The evaluation (often admittedly inaccurate) of the patient himself.

2. The reduction of the visible signs of scratching.

3. The repeated recurrence of the complaints and of scratching on withdrawal of the drug; and their renewed abatement on readministration.

It is necessary to state that, with the exception of most cases of urticaria, other topical medication was often used concomitantly with the antihistaminic drugs. However, the effectiveness of the antihistaminic agent could usually be gauged by a marked or rapid or prolonged reduction of itching and scratching over and above that achieved by the other remedies. On the basis of the above criteria our estimates of the antipruritic effects of Pyribenzamine in 124 cases are set forth in Table 1.

In addition to the 124 carefully studied cases treated with Pyribenzamine and presented in Table I, we have now had experience with several hundred more cases of itching dermatoses treated with Pyribenzamine or Benadryl. While these cases could not be as carefully evaluated as those presented in Table 1, the following are our estimates of the antipruritic efficacy of these two drugs on the basis of our total experience to date:

In the many different itching dermatoses (excluding cases of urticaria, but including cases of atopic dermatitis and eczematous dermatitis) antihistaminic drugs produced a striking * antipruritic effect in only 10 per cent. In an additional 35 per cent there was some † decrease in itching. In 55 per cent no antipruritic effect was noted.

In 75 per cent of cases of urticaria antihistaminic drugs produced a striking * antipruritic effect; and in 25 per cent no effect was noted.

In atopic dermatitis (in infants, children, adoles-

* "Striking" decrease in itching refers to a marked diminution of itching which was evident at all times during the administration of the drug.

† "Some" decrease in itching refers to a diminution of itching which was definite although varying from slight to considerable. Such action was either noted at all times while the drug was being administered to the patient or it was noted only during one or several exacerbations of the dermatosis.

cents and adults) antihistaminic drugs produced a striking * antipruritic effect in only 5 per cent of cases, in an additional 40 per cent there was some † decrease in itching, and in 55 per cent no effect was noted.

In eczematous dermatitis antihistaminic drugs produced a striking * antipruritic effect in 10 per cent of cases, in an additional 35 per cent there was some † decrease in itching, and in 55 per cent no effect was noted.

With the possible exception of pruritus vulvae and pruritus ani, no other dermatoses appeared to be especially susceptible to antipruritic management with antihistaminic drugs.

Difference in Effects of Pyribenzamine and Benadryl. We observed a number of patients in whom Benadryl was effective against itching or urticarial lesions when Pyribenzamine was not effective, and conversely patients in whom Pyribenzamine was effective while Benadryl was ineffective. Thus, when one of these drugs has failed, it is always warranted to try the other. As a rule, it was not possible to compare the antipruritic efficacy of Benadryl and Pyribenzamine in the same patients and no definite statement as to their relative efficacy can be made. However, Pyribenzamine is usually our drug of choice because of the greater tendency of Benadryl to produce undesirable side effects, especially in its greater soporific action.

DOSAGE

The dosage used in our cases has varied from 25 mg. three times daily to 50 mg. eight times daily. This wide range was due to the great variability in effective dosage from patient to patient. Thus, one patient with urticaria would respond to 25 mg. three times daily, while the next case required 50 mg. six times daily before any relief from itching was noted. The correct dose thus had to be ascertained in each individual case. As a rule we started our patients on 50 mg. three to four times daily and subsequently adjusted the dosage if this became necessary because of lack of beneficial effects or because of prohibitive side-effects. By and large there were no significant differences in the effective doses of Benadryl and Pyribenzamine.

In some cases one very helpful measure has been to arrange for a "heaping" of dosage during the night. It is well known that in many patients itching is much more severe during the night or that itching occurs only during the night. In such cases we told our patients to take 50 to 100 mg. of the antihistaminic drug before retiring and to take another 50 mg. if awakened during the night by the itching. In such situations Benadryl is sometimes to be preferred at night because of its greater soporific action; while Pyribenzamine may be preferable during the day when sleepiness should be avoided.

SIDE-EFFECTS

Among the 124 cases treated with Pyribenzamine and listed in Table 1, approximately 28 per cent of the patients experienced some side-effects. The variety and distribution of these manifestations are shown in Table 2.

TABLE 2

Side-Effects Exhibited Among 124 Cases Treated with Pyribenzamine

SIDE-EFFECT	CASES
Sleepiness	7
Nausea	7
Excitement, "jitteryness," "lightheadedness"	6
Headache	5
Urinary frequency	2
"Heartburn"	2
Reduction of potency	1
Diplopia	1
Feeling of cold	1
Dizziness	1
Sweating	1
Difficulty in urination	1

While the types of untoward manifestations observed from Benadryl and Pyribenzamine were quite similar, the incidence of side-effects from Benadryl appeared to be considerably higher than from Pyribenzamine. As previously remarked the number of patients who experienced sleepiness and dizziness from Benadryl was much greater than from Pyribenzamine, while the latter drug had a greater tendency to produce sleeplessness, stimulation, and "jitteryness." Both drugs, but particularly Benadryl, sometimes had a sufficiently strong sedative effect to make the administration of other sedatives unnecessary. Thus, in certain patients, we were able to eliminate other sedatives which are themselves sometimes causes of itching or skin eruptions, for instance, barbiturates and opium derivatives.

Untoward effects occurred as a rule at the beginning of the administration of the drugs, that is, within the first few hours to one or two days. In some patients in whom continuation of the medication appeared important but who complained of annoying side effects, we have at times observed an increase of tolerance when the dosage was first lowered to 12.5 or 25 mg. three times daily and then gradually in-

creased over a period of a week to ten days until the effective dosage was achieved.

There were only a few patients in whom the drugs had to be permanently discontinued because of the severity of the side-effects. *It was reassuring to note that the untoward manifestations in our cases were never of a serious or dangerous nature and that they readily disappeared usually within a few hours after discontinuing the drug.* The therapeutic effectiveness and side-effects appeared to be independent of each other, since those patients in whom side-effects were noted were not necessarily the same ones in whom the therapeutic effects were most manifest and vice versa.

For the first 18 months of our use of antihistaminic drugs we carried out blood counts and urinalyses approximately once weekly on all patients receiving these new preparations. We have not seen a single case with abnormal urinary or hematologic changes attributable to these drugs. Nevertheless the possibility of severe reactions in an exceptional case cannot be excluded as yet and it cannot be urged too strongly that these drugs, which must often be taken for lengthy periods, *should be dispensed only on prescription and taken while under competent medical supervision.*

SUMMARY AND CONCLUSIONS

1. The antihistaminic drugs, Pyribenzamine and Benadryl, are valuable adjuvants in the treatment of some cases of itching dermatoses.

2. A strong antipruritic effect is exerted in about 10 per cent of cases of itching dermatoses other than urticaria.

3. In urticaria, a strong antipruritic effect and reduction of the clinical lesions are noted in approximately 75 per cent of the cases.

4. The only itching dermatoses in which the antihistaminic drugs have a direct, grossly visible effect on the lesions are: urticaria (including urticarias due to drugs, to physical agents, etc.) and the associated urticarial lesions of other dermatoses.

5. In order to achieve maximum benefits with minimal side-effects, the choice of drug and dosage schedule must be adjusted to the individual case.

6. The antipruritic action of antihistaminic drugs and their action which produces side-effects appear to be independent of each other.

7. It is urged that this new class of drugs be dispensed only on prescription, and that all patients be kept under medical observation during the period of administration.

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Pneumonia Becoming a Minor Cause of Death

The mortality from pneumonia and influenza continues to decline rapidly and the prospects are that the two diseases, together, will be little more than a minor cause of death in the near future.

The gains against pneumonia and influenza in recent years have been truly remarkable. It is very likely that for the year 1947 the death rate from these two diseases will be about 25 per 100,000 among Metropolitan Industrial policyholders, all ages combined. Pneumonia and influenza as a group now rank eighth as a cause of death in this insurance experience, and account for less than 4 per cent of the total mortality. Only 10 years earlier, prior to the extensive use of serums and chemotherapy, these diseases were outranked only by heart disease and cancer, and were responsible for 10 per cent of the deaths from all causes combined. Had the trend for the years prior to 1937 continued to date, the current mortality rate would have been in the neighborhood of 60 per 100,000, or more than twice the rate that now prevails among these insured.

Every group among these insured, irrespective of age or sex, has benefited greatly from the marked improvement in mortality. In the past decade, declines of more than 70 per cent have been recorded at most age periods among both white males and white females; at ages 25 to 34 the reduction in each sex has been as much as 80 per cent. At no age period up to 75 years was the decrease less than 56 per cent between 1935–1936 and 1945–1946.

——From *Statistical Bulletin,* Metropolitan Life Insurance Company, 28:10, 1947.

Sprue is by no means confined to the tropics and it is likely that more mild or incomplete cases of the disease exist than is generally thought. Furthermore, as the author points out, sprue, or a sprue-like condition, may be at the bottom of some of the cases of multiple dietary deficiency seen in practice. These possibilities are more important now that it is possible with folic acid, not only to diagnose with greater certainty some of these obscure conditions but to provide permanent relief.

Diagnosis and Differential Diagnosis of Sprue

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The discovery of folic acid (Lactobacillus casei factor) has drawn more attention to the clinical picture of sprue. This symptom complex has been recognized as a distinct clinical entity since the publications of Manson from China and van der Burg from the Dutch East Indies in 1880. Although sprue was first considered to be a tropical disease, a gradually increasing number of reports of a similar condition found in the temperate zone—so-called nontropical sprue occurring in patients who have never been in endemic areas—shows that sprue is not restricted entirely to the tropics. There is no doubt that the disease will occur and be diagnosed in the United States more frequently than before. Because of the discovery of folic acid, more attention will be paid to the diagnosis of sprue. During the war and postwar period, many in the armed forces were and are still stationed in areas where sprue is an endemic disease.

The diagnosis is usually easy when the disease is in its advanced stage and presents a well-defined, characteristic and unmistakable symptom complex. Even in advanced cases, however, diagnosis may be difficult because symptoms of other deficiencies are superimposed and confuse the clinical picture. Far greater difficulty is experienced when the disease is in its early stage. Its gradual and insidious beginning, its remittent course, its sharing of the symptoms with other diseases and the lack of a trustworthy test characteristic only of sprue, make the diagnosis difficult. As there is not one single symptom characteristic of sprue alone, the diagnosis can be made only by a combination of the course of the disease and evaluation of the various symptoms and laboratory findings. In a number of cases dietary treatment and especially therapy with liver extract and folic acid are followed by such a dramatic and complete recovery that a diagnosis of sprue is indicated. But though the provisional diagnosis can be confirmed by the results of specific therapy, the diagnosis usually must be made from the clinical picture and the result of laboratory tests. It is of vital importance to recognize sprue in its early stages and to unmask it as a primary disturbance in multiple deficiencies because we are able today to treat many cases successfully and to cure a large percentage, provided therapy is started before permanent tissue damage has occurred.

SYMPTOMS

Fatty diarrhea, accompanied by meteorism and followed by emaciation, with remissions and acute relapses varying in intensity, must be regarded as the main and primary symptom. Stomatoglossitis, hypochromic and hyperchromic anemia are frequently encountered. There also occur symptoms of deficiencies of vitamins A, B_1, B_2, C, D, K and of such minerals as calcium and phosphorus.

Steatorrhea. The most striking and important of all the features of sprue is steatorrhea, usually accompanied by a diarrhea. Sometimes, although fortunately not often, constipation is present and distracts attention from the importance of a stool test. The presence of an increased quantity of fat in the stool, especially of fatty acids and soaps, is indispensable for the diagnosis of sprue. Special caution must be observed in the interpretation of the stool test. At the very outset of the disease, or during a remission, fecal fat may be only slightly increased. As sprue often develops following chronic diarrhea and begins gradually, it is not possible to say precisely at what point the preliminary diarrhea ends and when sprue itself sets in. Therefore, in dubious cases it is advisable to repeat the stool test at regular intervals. Furthermore, it must be remembered that the food of the patient must contain a certain quantity of fat in order

to ascertain by examination of the stool, the degree of failure in the process of fat splitting and assimilation. One must remember also that treatment with liver extract and perhaps also with folic acid may bring about an improvement or even disappearance of steatorrhea. Liver extract seems to contain a specific "antisprue factor" regulating fat absorption, possibly in connection with the adrenal cortex hormone.[1] The work on folic acid seems to show that this factor corrects impaired fat absorption in sprue and therefore may be considered the true "antisprue factor."

The normal fat content of the stool in healthy persons amounts to 5 or 10 per cent of the dry weight, although some authors regard as pathologic only a fat content above 20 or even 28 per cent. This stool fat derives not from unabsorbed food fat but from desquamated epithelial cells, intestinal bacteria and intestinal secretion. The daily fat evacuation in normal individuals is about 10 or 12 Gm. in 24 hours. In sprue the total fat output in 24 hours varies between 40 and 50 per cent of the dried matter and may go up to 70 or even 80 per cent. The total quantity of fat in sprue stools may amount to as much as 80 Gm. per day. A simple microscopic test is generally sufficient to demonstrate an increase of neutral fat or split fat products.

An increased fat output is known to occur in other pathologic conditions and, therefore, cannot be regarded as of decisive diagnostic significance. *Pancreatic lesions* (carcinoma, chronic pancreatitis and obstruction of the papilla of Vater) may bring about the elimination of large amounts of fat in the stools. The general clinical picture of sprue and such pancreatic disturbances may present features very much alike (chronicity, marked emaciation and debility, meteorism, hypochromic anemia and steatorrhea), but laboratory tests will lead to an exact diagnosis. The differentiation lies in the composition of the excess fat in the stools. In pancreatic fatty diarrhea the increased fat output is due to failure to split fat and the fat is, therefore, largely neutral fat. Such stools are iridescent or white or pale in color and very often, on cooling, show the neutral fat as an oily substance or in solidified masses. Stools in sprue, though sometimes showing a similar color, are usually frothy, more liquid, and do not manifest the presence of visible neutral fat. The increased fat in the stool in sprue is largely in the forms of fatty acids and soaps. In contrast to pancreatic lesions the neutral fat of the food is split in a normal way, but the split products are not absorbed. The ratio of neutral fat to split fat falls as low as 1:18 against 1:2 in the stool of normal individuals. This increase of split fat is due to impaired fat assimilation as the result of a dysfunction of the intestinal mucosa after previous intestinal infections, with subsequent poor absorption of the "antisprue factor" which regulates fat assimilation. In cases in which patients have been living on an inadequate diet, failure of fat absorption may be due to a true nutritional deficiency.

Failure of fat absorption in association with formed and diarrheal stools, as an isolated symptom, is not uncommon in the tropics. In most of the cases the deficient fat absorption lasts for a relatively short time, disappears entirely or shows relapses. Other cases gradually develop chronic diarrhea, meteorism, fatigue, loss of weight, stomatoglossitis and hypo- or hyperchromic anemia—in other words the unmistakable picture of sprue. Therefore, in cases of chronic diarrhea the test of the stool for steatorrhea should never be neglected. It seems fair to assume that this failure of fat assimilation represents one of the earliest symptoms of sprue and corresponds to the so-called pre-sprue condition.

Apart from the different nature of the fatty stools in pancreatic lesions and sprue, there are other symptoms and tests that easily differentiate the two conditions. Whereas in pancreatic diseases the pancreas juice generally fails to enter the intestine, in sprue there is no change in the amount of pancreatic enzymes in the duodenal content. For this reason fatty diarrhea of pancreatic origin gives stools which contain a large number of undigested muscle fibers, whereas in sprue azotorrhea is seen more seldom and never to the same extent. Another finding in the stool, strongly suggestive of a pancreas lesion but usually absent in sprue, is the imperfect digestion of carbohydrate. A high diastase content in blood and urine favors the diagnosis of a pancreatic lesion; in sprue there is no increase of pancreatic enzymes, either in the blood or in the urine. Hyperglycemia and glycosuria may occur in pancreatic disturbances if the islands of Langerhans are affected; in sprue a low blood sugar curve after glucose ingestion has found to be a fairly constant feature as well as a low blood fat curve after fat ingestion. An increased rate of basal metabolism should be interpreted as a symptom of sprue. Development of jaundice clarifies the situation in favor of a pancreatic lesion.

Much greater difficulty in differential diagnosis is encountered in the group of diseases which show defective fat absorption rather than failure of fat splitting. *Involvement of the mesenteric lymph system* (tuberculosis, malignancy and amyloidosis) may produce stools having a very close resemblance to the stools of sprue. Abdominal tuberculosis may affect

and obstruct the mesenteric glands and main lymphatic ducts with the result that fat already absorbed cannot be carried off through the lymph vessels. This mechanical obstruction results in congestion and subsequent failure of assimilation of the split fat. Further symptoms of such a tuberculous condition resembling sprue are marked emaciation, debility, distension of the abdomen, meteorism, hypochromic anemia and abdominal distress. However, there may be other symptoms to distinguish the two diseases. The past history of the patient usually reveals previous tuberculous manifestations, or an active tuberculous process elsewhere may be demonstrable. Fever, leukocytosis, a shift to the left of the neutrophiles and a high rate of blood sedimentation are suggestive of tuberculosis, whereas leukopenia, a relative lymphocytosis and normal sedimentation rate are characteristic of sprue. Ascites or palpable abdominal masses are unmistakable manifestations ruling out sprue. Hyperchromic anemia, glossitis, low blood sugar curve and high metabolic rate are indicative of sprue.

The same conditions as those in tuberculosis are found if the mesenteric lymph system is involved by malignant tumors or amyloidosis. However, in these cases it generally will be possible to diagnose the primary disturbance as the mesenteric lymph system is not involved until the primary lesion—either neoplastic or of the chronic infective type—has advanced to such a degree that it cannot be missed on careful examination.

A symptom complex, with fatty diarrhea similar to that of sprue and various other sprue symptoms such as stomatoglossitis, anemia and emaciation, can be seen in patients on whom *gastro-intestinal operations* have been performed. In these cases either most of the small intestine has been removed or, after gastroenterostomy, a gastro-jejuno-colic fistula has developed leading to a short-circuiting of the intestine. Most authors differentiate this clinical picture from actual sprue, but in essentials it is identical. For though in sprue the "antisprue factor" is missing in the diet or cannot be absorbed because of a functional disturbance of the intestinal epithelium, in these surgical cases short-circuiting or removal has put the small intestine out of function, thus leading to poor absorption of the "antisprue factor" and resulting in the sprue symptom.

Stomatoglossitis. Besides the leading sprue symptom, fatty diarrhea, the other manifestations such as glossitis, anemia of hypochromic and hyperchromic nature, and edema are frequently to be observed. Although stomatoglossitis is generally regarded as a cardinal sprue symptom, it seems questionable whether we have the right to consider it a primary manifestation of sprue. The same oral changes are also met in pellagra, pernicious anemia and ariboflavinosis. At the beginning of the disease inflammatory changes are seen, especially at the tip and along the edges of the tongue. Eventually, the tongue becomes atrophic and looks varnished. The oral cavity may likewise be affected. Cases in which stomatoglossitis precedes the development of the classical sprue picture by months or years are classified by Manson-Bahr [2] as "tongue or mouth sprue." However, such an isolated stomatoglossitis is generally curable by nicotinic acid or riboflavin. The fact that glossitis in sprue is cured by liver extract can easily be explained by the nicotinic acid, riboflavin and folic acid content of some liver extracts. In some cases, steatorrhea, anemia and the other symptoms of sprue may improve considerably without the tongue showing any improvement at all, or, even after a successful treatment, stomatitis may recur as an isolated morbid manifestation. We must assume that stomatoglossitis in sprue is a secondary symptom and that an isolated deficiency of one or the other factor of the vitamin B_2 group (riboflavin, nicotinic acid or folic acid) may remain or recur due to an impaired absorptive power of the small intestine.

Hyperchromic Anemia. The question of the significance of hyperchromic anemia as a symptom of sprue has raised lively discussion in the literature of the disease. As a matter of fact, the anemia of sprue in many advanced cases offers a picture almost indistinguishable from that in Addisonian pernicious anemia. Blood tests in either disease reveal hyperchromic macrocytic anemia with a color index above 1, leukopenia and relative lymphocytosis. The Price-Jones curve of the red blood cells and the findings of sternal puncture in sprue correspond to those in pernicious anemia. The identity of both forms of anemia seems to be possible, especially as either reacts to liver and folic acid therapy with a similar reticulocyte response and striking improvement of the red blood cell picture.

Of further similar symptoms, sore tongue and mouth and subacute combined degeneration of the cord have to be mentioned, although the latter is seen less often in sprue than in Addisonian anemia. Histamine refractory achylia can also be demonstrated, but in sprue it does not constitute as constant a symptom as in pernicious anemia. The similarity of the picture is sometimes so striking that, because of the hematologic findings, the two diseases were at one time declared identical by Castle and Rhoads.[3]

If, however, one has seen a great number of patients with sprue and has kept them under close ob-

servation for many years, one comes to the conclusion that the two conditions cannot be identical, although the resultant anemia may be almost the same. There are certain differences, even hematologically, though nowadays the interpretation of the blood picture may be difficult as most sprue patients have had some liver or folic acid treatment before an exact diagnosis is made. In sprue, normoblasts are seen less often than in primary Addisonian anemia and megaloblasts can rarely be demonstrated. In the initial stage of sprue there is mostly a hypochromic microcytic anemia which is due to iron deficiency. It changes to a hyperchromic macrocytic anemia with the progress of the disease. A reversal from hyperchromic anemia to the hypochromic form is also met with, even in the same individual. Addisonian anemia only improves after administration of the intrinsic factor in the form of stomach preparations, liver extract or folic acid, whereas in sprue improvement of the red blood cells and hemoglobin can be obtained by other means. If in sprue dietary treatment succeeds in checking diarrhea and steatorrhea, an improvement of the red blood picture may take place; pernicious anemia never reacts to dietary treatment. Once the diagnosis of Addisonian anemia is established, treatment is necessary for the patient's life as permanent cure of the disease is unknown. In sprue erythropoiesis becomes and remains normal when the disease is cured, although anemia may recur in the event of a relapse of the intestinal symptoms.

Besides these differences, there are other laboratory findings distinguishing the two diseases from each other. In Addisonian anemia, owing to destruction of red blood cells, the bilirubin content of the blood is increased, and both stools and urine show an increase of urobilin and urobilinogen. In cases of sprue the blood, stool and urine tests are negative. The flat glucose tolerance curve and the low blood fat curve after fat ingestion, often encountered in sprue, cannot be demonstrated in pernicious anemia. A decrease in calcium, phosphorus and various vitamins in the blood occurs in advanced cases of sprue but not in pernicious anemia. Diarrhea may be seen in Addisonian anemia as the result of gastric achylia, but the stool never shows an increased fat content. The combination of hyperchromic anemia and failure of fat absorption points almost infallibly to a diagnosis of sprue. Difficulties in diagnosis may arise in cases where steatorrhea is not combined with diarrhea. An erroneous diagnosis of pernicious anemia may then be made because the stool test has been neglected. It seems very probable that the few published cases of Addisonian anemia with free acidity in the stomach juice were really suffering from sprue. In all cases of suspected pernicious anemia the examination of the stool for split fats should be as much an obligatory test as the examination of the stomach juice. The demonstration of free acidity in the stomach juice and the presence of an increased quantity of split fat in the stool rules out primary Addisonian anemia and is strongly suggestive of sprue. The function of the gastric mucosa may show a marked difference in its reaction to therapy. Histamine refractory achylia is a permanent symptom in pernicious anemia, even in spite of successful therapy. In sprue when achylia is encountered the function of the mucosa of the stomach may become normal again with the improvement of the disease.

There are other general symptoms indicating that the two conditions are not identical. Patients with Addisonian anemia are pale or show a characteristic lemon-yellow tint or a distinct subicteric change of the skin or sclera, whereas the skin of sprue patients is pale-grayish, yellowish-brown or muddy in color. The emaciation and the intense weakness, so characteristic of sprue, are not observed in Addisonian anemia to nearly so marked a degree in cases with comparable blood counts, and the distended abdomen and the distressing meteorism are not encountered at all.

A question arises as to which pathologic condition in sprue causes the disturbance of erythropoiesis. The most likely explanation is that, due to the fermentation in the small intestine and its impaired absorptive power folic acid is destroyed or not absorbed. Subsequently, as a secondary symptom, a condition develops similar to Addisonian anemia. Such a conception would explain why improvement of the intestinal symptoms in cases of sprue is followed by normal blood formation, even without any medication. If folic acid is given therapeutically, enough of it is absorbed to insure normal blood formation. It is of interest to note that recently Spies and his associates [4] proposed a hypothesis that the pathogenesis of macrocytic anemia of sprue differs from that of Addisonian anemia.

Edema. Among the secondary manifestations occurring in sprue, edema should be mentioned. These swellings are not of cardiac or renal origin. There is no cyanosis, dyspnea or albuminuria. No improvement is seen after rest in bed or administration of digitalis. The edema may be transitory or remain for some time, even after the other sprue symptoms have been brought under control. Sometimes it develops after these symptoms have already shown marked improvement. This edema represents a secondary deficiency symptom the nature of which is not yet clear.

Multiple Deficiency. Besides the symptoms already mentioned, various others may occasionally develop simultaneously and present an apparent picture of a complex deficiency state. Nearly all known vitamins and various minerals have been reported as decreased in the blood of patients with sprue.[5] Symptoms of scurvy, ariboflavinosis, deficiency in vitamins A, B_1, D, K, and in calcium and phosphorus have been noted, either singly or in combination. Sprue then may present the most complex and polymorphous of all deficiency states and sometimes the secondary symptoms are in the foreground of the clinical picture to such an extent that the primary symptoms of sprue are overshadowed. These secondary manifestations may sometimes be due to dietary inadequacy but mostly develop when the intestinal dysfunction produces a faulty absorption of other essential factors than the "antisprue factor." It is for this reason that, in spite of a normal diet which may be even rich in vitamins, deficiency of various factors may occur. In cases of multiple deficiency one should always think of sprue as a possible underlying primary disturbance. Benett, Hunter and Vaughan[6] have characterized the paradoxical condition of such patients in the apt words "they are starving in the midst of plenty."

DISEASES RESEMBLING SPRUE

Pellagra. The picture of pellagra may seem very similar to the symptom complex of sprue. In either disease, glossitis, diarrhea, anemia, progressive weakness, pigmentations and psychosis are to be seen. However, there is no increased fat output in pellagra. Hypochromic anemia is seen in either condition, hyperchromic anemia generally only in sprue. Dermatitis, especially of symmetrical nature is suggestive of pellagra; in sprue pigmentation of the skin may be noted, clearing up with the improvement of the disease and recurring with its return. Severe psychosis or dementia must be rated as signs of pellagra although in sprue irritability and depression are quite frequent. Differential diagnosis is difficult in border-line cases which are by far more frequent than is generally assumed.

Addison's Disease. Another disease with a certain similarity to sprue is Addison's disease. Both conditions are associated with vomiting, diarrhea, extreme weakness, marked loss of weight, pigmentations, apathy, depression, anemia and hypotony. In recent years there have been increasing reports of patients with Addison's disease who show an impaired fat assimilation similar to sprue. Such a steatorrhea in Addison's disease would be in accordance with Verzár's[7] theory that the hormone of the adrenal cortex regulates fat metabolism. In such cases the diagnosis may be extremely difficult. Hyperchromic anemia must be regarded as a symptom of sprue; in Addison's disease polycythemia may occasionally be seen due to a decrease in the blood volume and hemoconcentration. Pigmentation in Addison's disease is seen in the skin and mucous membrane; in sprue, pigmentation of the skin is sometimes seen, but never in the mucous membrane. In dubious cases blood and urine tests will solve diagnostic difficulties. In Addison's disease an increase in the blood urea and a decrease in the sodium content of the blood are of diagnostic importance; also, an increase in sodium chloride and creatinine in the urine. In advanced sprue, as the result of a faulty absorption of protein, hypoproteinemia, a low calcium and phosphorus content of the blood and an increase in the indican in blood and urine are found.

Tuberculosis or Malignancy of the Intestines. Finally, there are some conspicuous points of resemblance between the clinical features of sprue and tuberculosis or malignant tumors of the intestines. As in sprue, indigestion, meteorism, debility, chronic diarrhea, emaciation, hypochromic anemia and edema may be seen in these conditions. However, the stool tests do not reveal steatorrhea unless the mesenteric lymph system is involved. A marked difference in the appetite can be noted. In the majority of cases of sprue appetite is normal or even ravenous, in tuberculosis or malignancy anorexia is usually present. Hyperchromic anemia and, generally, glossitis are absent in tuberculosis and malignancy. Sprue is not associated with fever, leukocytosis, an increase in the polymorphonuclears and a shift to the left of the neutrophiles. Other points of difference have been mentioned above. The x-ray examination in sprue reveals an accumulation of barium in dilated coils of the intestines, a coarse mucosal pattern and a slow progress of the opaque meal. In difficult cases, x-ray examination of the intestines and the presence of tubercle bacilli in the stool will help clarify the diagnosis.

SUMMARY

The main and primary symptom of *sprue* is steatorrhea due to impaired absorption of the split fat products. Steatorrhea in *pancreatic* lesions is the result of deficient splitting of fat. Other symptoms in which the two conditions differ have been discussed.

Defective fat absorption similar to that in sprue is seen when the mesenteric lymph system is involved by

tuberculosis, malignancy or amyloidosis, but in such cases there are other symptoms present to differentiate them from sprue.

Steatorrhea, with a symptom complex similar to sprue, occurs after gastro-intestinal operations with short-circuiting of the small intestine and must be regarded as identical to that occurring with sprue.

Stomatoglossitis, hypo- and hyperchromic anemia and edema are common secondary manifestations of sprue.

Stomatoglossitis is attributed to a deficient absorption of one or another of the fractions of the vitamin B complex, nicotinic acid, riboflavin and folic acid. Hyperchromic anemia in sprue differs from that of pernicious anemia in regard to its pathogenesis; their differential diagnosis is discussed. Edema presents a deficiency state.

The difficulty of diagnosis in cases of sprue with manifestations of a multiple deficiency is stressed.

The similarity of pellagra, Addison's disease and tuberculosis or malignancy of the intestines to sprue and their differential diagnosis are discussed.

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MEDICINE IN THE NEWS . . .

HYDRILLIN

Recent references in the lay press to hydrillin (hydryllin) as a new antihistamine drug, or the latest synthetic drug for the treatment of certain allergic states, should not mislead physicians. As is often the case, the rapid development of a new group or series of compounds useful in treatment is apt to be confusing. Substances of closely similar composition and with closely similar properties are given individual names. Often these are not descriptive and, in fact, a fully descriptive name may be difficult to give or to use. Various preparations of the substance are prepared and these, too, may be named individually. Combinations with other substances to obtain actual or anticipated improvement or modification of action or additional desirable effects may be attempted.

In the case of hydryllin, the antihistamine agent is none other than diphenhydramine, the active base contained in diphenhydramine hydrochloride. This substance is listed in *New and Non-official Remedies* and is identical with benadryl hydrochloride (Parke-Davis). Diphenhydramine is, of course, widely used in this country and was one of the first antihistamine drugs of this type.

In hydrillin (hydryllin), the antihistaminic drug is combined with aminophylline (USP). The evidence available suggests that the two substances are merely additive in their antihistaminic action and are not synergistic. Aminophylline is useful in asthma and from this it might be inferred that it might have some effect in other allergic states. However, it is also helpful (intravenously) in paroxysmal dyspnea or pulmonary edema of cardiac origin which presumably is not allergic in nature.

Conclusions regarding the advantages of a combination of diphenhydramine with aminophylline will require careful clinical observation.

The beeswax, peanut oil, penicillin mixture provides for slower absorption of the active agent. It is essential that the physician using this have some knowledge of the penicillin blood levels in the hours following injection. This paper provides such information.

Serum Concentrations of Penicillin Following Administration of Crystalline Penicillin G in Peanut Oil and Beeswax*

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The incorporation of salts of amorphous penicillin in a mixture of peanut oil and beeswax has been demonstrated to be a satisfactory method for delaying the absorption of penicillin when administered intramuscularly or subcutaneously.[1-4] Following a single injection of 300,000 units of amorphous calcium penicillin in 4.8 per cent beeswax (by weight) and peanut oil, penicillin is detectable in the blood for 24 hours following administration in about 70 to 75 per cent of the group of individuals tested. Assayable amounts of penicillin are present in the blood in practically all cases for 12 hours following administration. The maximum concentration of penicillin obtained in the serum following injection of 300,000 units of calcium penicillin in peanut oil-beeswax varies usually from 0.078 to 2.5 units per cubic centimeter.

The purpose of this report is to present pharmacologic data concerning the absorption of sodium and potassium salts of crystalline penicillin G suspended in a mixture of peanut oil and beeswax. Information is presented concerning the use of various dosage schedules and the influence of varying the volume of peanut oil and beeswax in which a given dose of penicillin is administered, as well as the effect of dividing a given dosage between two simultaneous sites of injection.

MATERIALS AND METHODS

Antibiotic Agents. The sodium and potassium salts of crystalline penicillin G suspended in peanut oil with 4.8 per cent (by weight) bleached beeswax were available in concentrations of 300,000 units per cubic centimeter and 550,000 to 600,000 units per cubic centimeter.† The viscosity of the preparations of crystalline potassium penicillin G was considerably less than the preparations containing crystalline sodium penicillin G.

Method of Administration of Penicillin in Peanut Oil and Beeswax. The schedules of administration employed were designed to reveal, (1) the serum penicillin levels following a single injection of 300,000 units and of 600,000 units, (2) the effect on the serum penicillin concentration of the volume of peanut oil and beeswax in which a given dosage of crystalline penicillin G was administered, and (3) the effect on the serum penicillin concentration of dividing a given dose between two sites simultaneously injected. The following schedules were employed with each of the crystalline salts available administering the dosage indicated once per 24 hours except in (f) as indicated:

a. One cubic centimeter peanut oil and beeswax containing 300,000 units crystalline penicillin G.

b. One cubic centimeter peanut oil and beeswax containing 600,000 units crystalline penicillin G.

c. Two cubic centimeters peanut oil and beeswax containing 600,000 units crystalline penicillin G.

d. One cubic centimeter peanut oil and beeswax containing 300,000 units crystalline penicillin G injected at two sites simultaneously.

e. One half cubic centimeter peanut oil and beeswax containing 300,000 units crystalline penicillin G injected at two sites simultaneously.

f. One cubic centimeter peanut oil and beeswax containing 300,000 units crystalline penicillin G at 12-hour intervals.

These preparations were easily administered in the conventional manner. The rubber-capped bottle con-

* From the Evans Memorial, Massachusetts Memorial Hospitals and The Department of Medicine, Boston University School of Medicine.

This study was supported in part by a Grant-in-Aid from The Squibb Institute of Medical Research, New Brunswick, New Jersey.

† We are indebted to E. R. Squibb and Sons, New Brunswick, New Jersey, for supplying the crystalline penicillin G in peanut oil and beeswax employed in these studies.

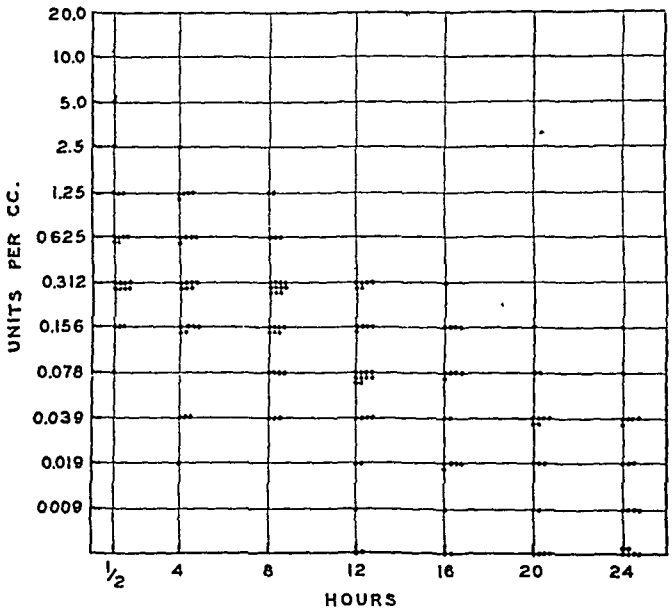


FIG. 1. Serum penicillin concentrations following a single dose of one cubic centimeter of peanut oil and beeswax containing 300,000 units crystalline sodium penicillin G.

taining the mixture of penicillin in peanut oil and beeswax was placed in water at about 60° for about five minutes. After this the mixture became quite fluid and was easily withdrawn into a dry, sterile syringe with an 18- or 20-gauge needle. Another 20-gauge needle was used for intramuscular administration and was inserted on an empty, dry, sterile syringe with which it was possible to ascertain that the needle was not in a blood vessel. The mixture of penicillin in peanut oil and beeswax could then be easily injected through this needle by changing syringes leaving the needle in place. Administration of the mixture in disposable cartridges containing one cubic centimeter eliminated the necessity of warming the mixture inasmuch as it was sufficiently liquid at room temperature to inject without difficulty.

Experimental Subjects. Adult male and female human subjects were used who presented no evidence of impaired renal, cardiac, or liver function. Most of the subjects were normal postpartum females or young adults convalescing from various types of acute illness.

Method for Determination of Serum Penicillin Concentrations. Using sterile precautions venous blood was drawn one half hour after administration of crystalline penicillin G in peanut oil and beeswax and at intervals of four hours after injection for a period of 24 hours. The serum penicillin concentrations were determined by the method described by Rammelkamp.[5]

RESULTS AND COMMENT

Administration of 300,000 Units of Crystalline Sodium Penicillin G. Thirty subjects received intramuscularly one cubic centimeter of peanut oil and beeswax containing 300,000 units of crystalline sodium penicillin G. Ten of these individuals were given a second injection of 300,000 units 12 hours later. The serum concentrations of penicillin during the 24 hours following administration of a single dose of 300,000 units of this preparation are shown in Figure 1. In 23 instances the serum concentration of penicillin was determined one half hour following administration and varied from 0.078 to 5.0 units per cubic centimeter serum with 19 of the 23 subjects having a concentration of at least 0.31 unit per cubic centimeter serum. The maximum levels obtained with this dosage occurred uniformly during the first eight hours following injection and varied from 0.31 to 5.0 units per cubic centimeter serum. The maximum level obtained following a given injection persisted for 12 hours following administration in only one instance. Twelve hours following this injection 28 of the 30 subjects had concentrations of penicillin in the serum varying from 0.009 to 0.312 unit per cubic centimeter serum with 21 patients (70 per cent) having levels of at least 0.078 unit per cubic centimeter serum. Assayable amounts of penicillin were present in the serum 24 hours following administration of a single dose of 300,000 units in 14 of 20 patients (70 per cent) and varied from 0.009 to 0.156 unit per cubic centimeter serum. These levels are, thus, quite similar to those obtained with a suspension in similar medium of amorphous calcium penicillin.

Administration of 600,000 Units of Crystalline Sodium Penicillin G. Nine subjects received intramuscularly one cubic centimeter of peanut oil and beeswax containing 600,000 units of crystalline sodium penicillin G. The range of concentrations of penicillin present in the serum of these patients during the 24 hours following administration is shown in Figure 2. One half hour following administration the serum contained 1.25 to 5.0 units per cubic centimeter serum and in only one case was the one-half-hour level exceeded during the following 24 hours. The maximum serum concentration occurred in all instances during the first four-hour period following administration and ranged from 0.625 to 20.0 units per cubic centimeter serum. The maximum level which occurred in a given individual during the first four hours following injection was present eight hours following injection in two cases and 12 hours following administration in one case. The serum concentration of

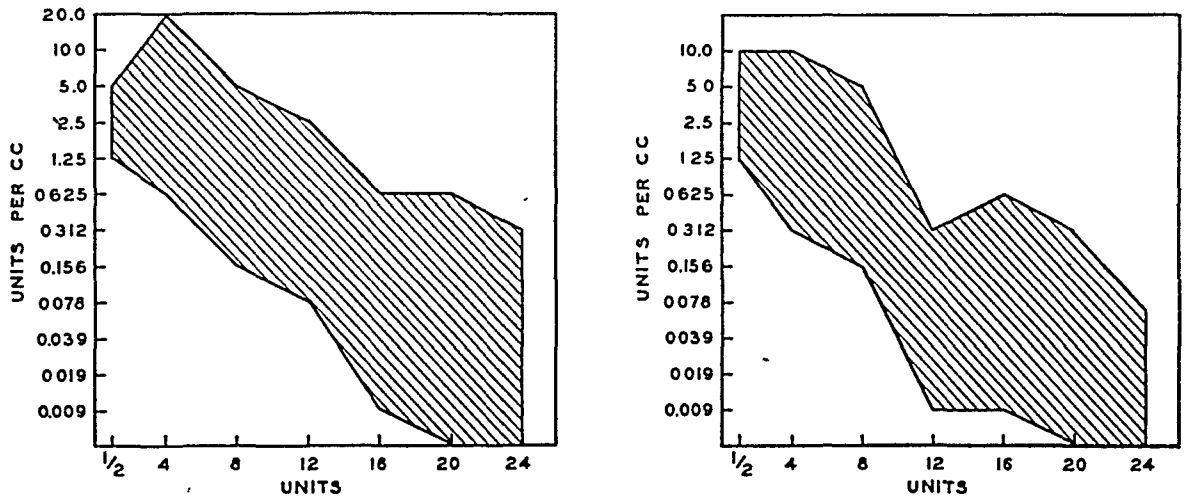


FIG. 2. Serum penicillin concentrations following administration of one cubic centimeter peanut oil and beeswax containing 600,000 units of crystalline sodium penicillin G. (*Left*) One cubic centimeter at one site of injection. (*Right*) One half cubic centimeter at each of two sites of injection.

penicillin 12 hours following injection of this dose varied from 0.078 to 2.5 units per cubic centimeter serum and 24 hours following administration seven of the nine patients showed at least 0.039 unit per cubic centimeter serum with five of the nine patients maintaining levels of at least 0.156 unit per cubic centimeter serum.

When the one cubic centimeter of peanut oil and beeswax containing 600,000 units of crystalline sodium penicillin G was divided equally between two sites of intramuscular injection in six additional subjects no appreciable difference was noted during the first 12 hours following injection as shown in Figure 2. The serum penicillin concentrations 12 and 24 hours after administration were, however, 0.009 to 0.312 unit per cubic centimeter serum and 0.00 to 0.078 unit per cubic centimeter serum respectively with three of the six patients failing to show assayable amounts of penicillin 24 hours following administration.

Administration of 600,000 units of crystalline sodium penicillin G in a volume of two cubic centimeters was also undertaken by injecting the total volume at one intramuscular site and by dividing the dose equally between two intramuscular sites. The range of serum penicillin concentrations in 14 patients following injection of the material at a single site is shown in Figure 3. In six cases serum penicillin determinations were performed one half hour after injection of the peanut oil and beeswax and values of

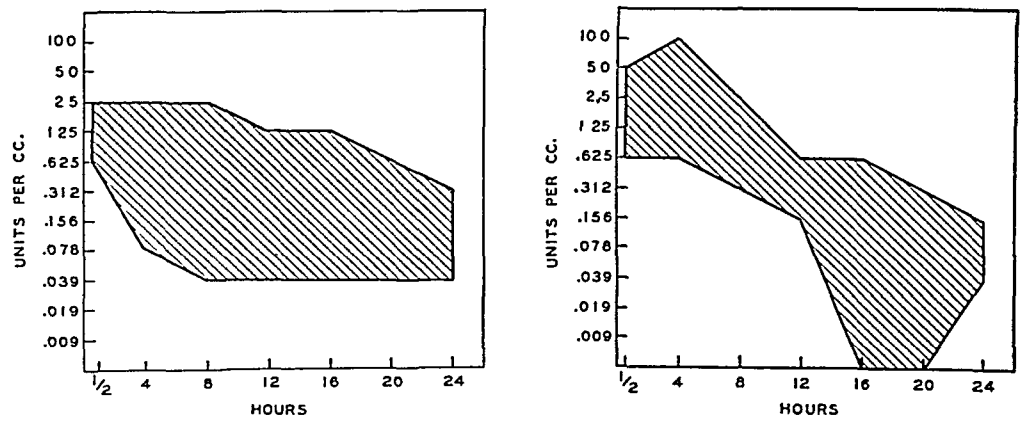


FIG. 3. Serum penicillin concentrations following administration of two cubic centimeters of peanut oil and beeswax containing 600,000 units of crystalline sodium penicillin G. (*Left*) Two cubic centimeters at one site of injection. (*Right*) One cubic centimeter at each of two sites of injection.

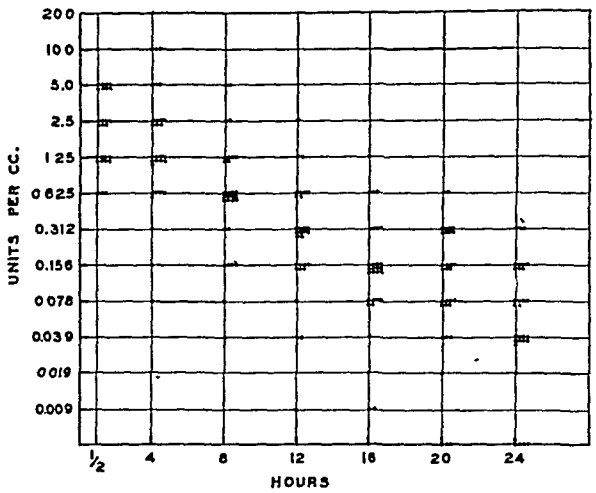


FIG. 4. Serum penicillin concentrations following administration of 600,000 units crystalline penicillin G in peanut oil and beeswax employing various methods of injection.

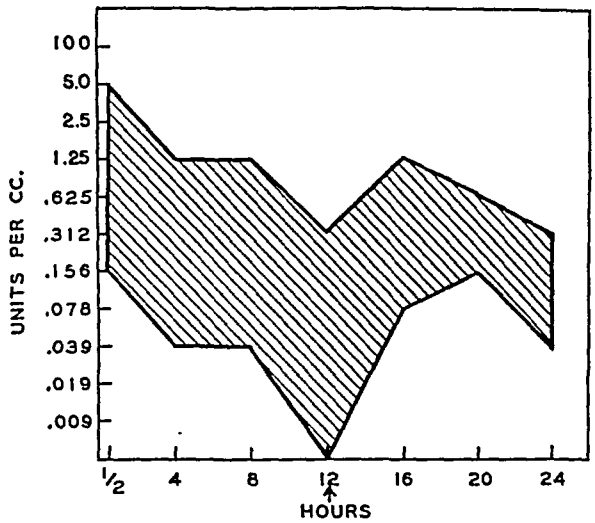


FIG. 5. Serum penicillin concentrations following administration of one cubic centimeter of peanut oil and beeswax containing 300,000 units crystalline sodium penicillin G at 12-hour intervals.

0.625 to 2.5 units per cubic centimeter serum were found. In three of these the level at one half hour was as high as at any time during the 24 hour period. Maximum levels varied from 0.078 to 2.5 units per cubic centimeter serum with the maximum level in a given individual persisting in four instances for eight hours and in one instance for 12 hours after administration. The serum penicillin concentration at 12 hours varied from 0.039 to 1.25 units per cubic centimeter serum and at 24 hours from 0.039 to 0.312 unit per cubic centimeter serum with seven patients (50 per cent) having levels of at least 0.156 unit per cubic centimeter serum at 24 hours. Dividing the two cubic centimeters of peanut oil and beeswax containing 600,000 units of crystalline sodium penicillin G between two sites of intramuscular injection in six patients resulted in serum penicillin concentrations which were comparable to those following utilization of a single site for injection although 24 hours after administration of the material at two sites only one patient manifested a serum penicillin concentration of 0.156 unit per cubic centimeter serum (Fig. 3).

The serum penicillin concentrations obtained following injection of 600,000 units of crystalline sodium penicillin G in peanut oil and beeswax on various dosage schedules are summarized in Figure 4. The concentrations occurring during the eight hours following injection of 600,000 units were significantly higher than after 300,000 units with 64 per cent of the determinations being over 1.0 unit per cubic centimeter in the former case as contrasted with 14 per cent over 1.0 unit per cubic centimeter in the latter. During this same period the minimum concentrations with the larger dosage were also of higher magnitude with 12 per cent of the determinations being less than 0.156 unit per cubic centimeter after 300,000 units as compared with 3.4 per cent of the determinations being less than 0.156 unit per cubic centimeter following the larger dosage. It is apparent from the serum penicillin concentration existent one half hour after administration of crystalline penicillin in peanut oil and beeswax that an adequate therapeutic level is readily obtained following injection and that under the usual circumstances no lag in absorption occurs which might require penicillin in aqueous solution at the time chemotherapy is initiated. When the serum penicillin determinations are plotted on semilogarithmic co-ordinates the rate of fall is approximately the same with either 300,000 or 600,000 units. The volume of emulsion in which a given dose is administered does not appear to affect appreciably the height of serum penicillin concentration obtained nor the uniformity of absorption. Administration of 600,000 units of crystalline sodium penicillin G divided equally between two simultaneous sites of injection produced higher maximum levels with 58 per cent of 12 patients manifesting levels of 5.0 to 10.0 units per cubic centimeter at some time during the eight hours following injection as contrasted with 18 per cent of 22 patients who received this dose at a single site. These levels are only present, however, during the first eight hours following injection and a somewhat more rapid rate of fall characterizes the serum penicillin concentrations following administration at two sites. The subjects receiving

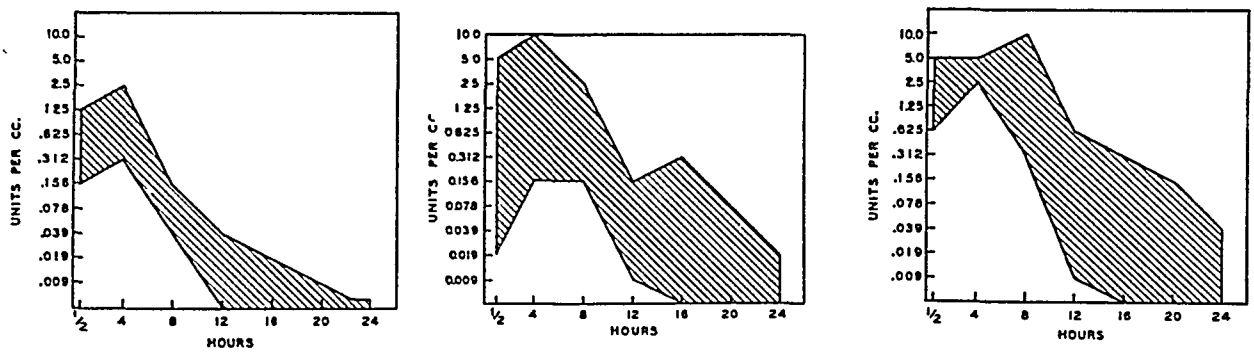


FIG. 6. Serum penicillin concentrations following administration of crystalline potassium penicillin G. *(Left)* One cubic centimeter containing 300,000 units. *(Center)* One cubic centimeter containing 600,000 units. *(Right)* Two cubic centimeters containing 600,000 units.

this dosage divided between two sites of injection manifested lower serum penicillin concentrations 24 hours after administration inasmuch as 25 per cent of these individuals failed to show assayable amounts of serum penicillin as contrasted with only nine per cent of the subjects receiving the total dose at one site. Furthermore, 55 per cent of the subjects receiving the 600,000 units at a single site maintained levels of at least 0.156 unit per cubic centimeter 24 hours after injection as contrasted with only eight per cent of the subjects receiving the penicillin at two sites of injection.

Administration of 300,000 Units Crystalline Sodium Penicillin G at 12-Hour Intervals. Ten patients were given a daily intramuscular dose of 600,000 units of crystalline sodium penicillin G in peanut oil and beeswax by administering one cubic centimeter containing 300,000 units at 12-hour intervals (Fig. 5). Twenty-four hours after the first injection of 300,000 units and 12 hours after the second injection of 300,000 units the serum penicillin concentration varied from 0.039 to 0.312 unit per cubic centimeter serum, with six subjects (60 per cent) having levels of at least 0.156 unit per cubic centimeter serum.

The serum penicillin concentrations which resulted from injection of 300,000 units of crystalline sodium penicillin G at 12-hour intervals were not of as great magnitude at any time as those following administration of 600,000 units in a single daily injection with only one patient (ten per cent) showing a concentration over 1.25 units per cubic centimeter on the former dosage schedule as compared with 20 patients (57 per cent) on the single daily injection schedule. However, 24 hours after initiation of penicillin therapy 60 per cent of the subjects receiving injections at 12-hour intervals maintained levels of at least 0.156 unit per cubic centimeter as compared with 32 per cent of the subjects receiving a single daily injection.

Administration of 300,000 Units Crystalline Potassium Penicillin G. The administration of one cubic centimeter of peanut oil and beeswax containing 300,000 units of the potassium salt of crystalline penicillin G to five patients produced serum penicillin concentrations during the first four hours after injection varying from 0.156 to 2.5 units per cubic centimeter serum (Fig. 6). No penicillin could be demonstrated in the serum of two of the five patients 12 hours after administration and 24 hours after injection none of the subjects manifested a demonstrable concentration of serum penicillin.

Administration of 600,000 Units Crystalline Potassium Penicillin G. The injection of 600,000 units of crystalline potassium penicillin G at a single site in a volume of one cubic centimeter to eight subjects and in a volume of two cubic centimeters to 12 subjects produced serum penicillin concentrations as shown in Figure 6 (center and right). Division of this dosage into equal portions of 0.5 cubic centimeter and one cubic centimeter for simultaneous administration at two sites produced serum penicillin concentrations as described below. Twenty-three of 29 patients had serum penicillin determinations one half hour after injection of this dosage and manifested serum penicillin concentrations ranging from 0.312 to 5.0 units per cubic centimeter serum with one exception (0.019 unit per cubic centimeter serum). The maximum levels obtained varied from 0.156 to 10.0 units per cubic centimeter serum and this maximum persisted for eight hours after injection in only five of the 29 subjects. Twelve hours after administration the serum penicillin concentration ranged from 0.009 to 0.625 unit per cubic centimeter serum with six patients having levels of 0.0919 unit per cubic centimeter serum or less. Twenty hours after injection the highest serum concentration observed was 0.156 unit per cubic centimeter serum with nine patients (31 per cent) having

no demonstrable penicillin in the serum and 24 hours after injection 14 subjects (48 per cent) failed to show assayable quantities of serum penicillin.

The serum penicillin concentrations following administration of crystalline potassium penicillin G were characterized by a much greater rate of fall than following administration of the crystalline sodium salt. No significant difference was observed in the maximum serum levels obtained during the first four hours after administration of similar dosages of the sodium and potassium salts of penicillin G but none of the subjects receiving 300,000 units maintained a demonstrable serum penicillin concentration at 24 hours, and 48 per cent of the subjects receiving 600,000 units failed to show assayable quantities of penicillin in the serum 24 hours after injection. These results have been confirmed in dogs by other workers using the same preparation.[6] A recent report indicated results diametrically opposed to the above, namely, a superiority of the potassium salt over the sodium salt.[4] These results may well be reconciled on the basis of the physical properties of the preparation administered inasmuch as the emulsion containing crystalline potassium G employed in these experiments was considerably more fluid than the emulsion containing crystalline sodium penicillin G.

Muscular activity may be a factor in absorption of penicillin in peanut oil and beeswax. In ambulatory patients the serum penicillin concentration frequently was observed to rise sharply following resumption of activity after sleep during the night.

Local Reactions to Crystalline Penicillin G in Peanut Oil Beeswax. Slight to moderate pain occurred frequently at the time of administration of this mixture and occasionally persisted for 24 to 48 hours. In only two of about 200 injections was a persistent nodule palpable at the site of injection probably due to administration of the mixture subcutaneously instead of intramuscularly. No allergic reactions were noted following administration of these preparations.

SUMMARY

1. Administration of 300,000 units of crystalline sodium penicillin G in peanut oil and beeswax produces demonstrable serum penicillin concentrations at 12 hours after administration in practically all cases and at 24 hours after administration in 70 per cent of cases.

2. A single injection of 600,000 units of crystalline sodium penicillin G in peanut oil and beeswax produces assayable serum penicillin concentrations 24 hours after administration in 86 per cent of cases.

3. Equal division of a given dosage of penicillin in peanut oil and beeswax between two sites simultaneously injected produces higher maximum levels during the first eight hours after administration but results in a shorter duration of assayable concentrations of penicillin in the serum.

4. The volume of peanut oil and beeswax as employed in these experiments in which a given dosage of penicillin is administered does not affect appreciably the height or duration of the serum penicillin concentration.

5. Division of a given daily dose of penicillin into two injections given at 12-hour intervals rather than in a single daily injection results in maximum levels of lower magnitude, but insures a more uniform serum penicillin concentration at all times than with the employment of a single daily dose.

We are indebted to Miss Doris McCarthy for technical assistance.

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The author reviews the management of acute infection of various types in the nervous system.

The Treatment of Acute Infections of the Nervous System

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PHILADELPHIA, PENNSYLVANIA

The acute infections involving the nervous system include a large group such as poliomyelitis, true myelitis, encephalitis, infectious polyneuritis and herpes zoster which are known to be, or are thought to be, virus in origin. For these the therapy up to now has been nonspecific and symptomatic. In addition some physicians recommend the use of the sulfones and penicillin to inhibit secondary invaders. While there is some point in this, it is hardly justification for the waste of these adjuncts in these cases.

Encephalitis is so seldom seen except in epidemics that it can receive only passing mention. These patients may require hypertonic enemas, hypertonic solutions intravenously and spinal drainage for the relief of headache and other symptoms of increased intracranial pressure. The latter should of course be proved by a pressure determination at lumbar puncture. A recent report of the use of a vaccine in the prevention of one type of encephalitis is a step in the right direction. This requires much further study and assay before its value can be determined.

True myelitis is again a rare entity. When nonvirus in origin as proved by culture, the appropriate drugs are of course to be used, otherwise the indications are to protect the patient from contractures, bed sores and ascending urinary infection. To these ends the bed clothes should be kept from bearing down on the dorsum of the feet by a cradle. The development of foot-drop and other deformities must be combatted by splints or sand-bags, the patient being turned from side to side as well as on his back every two hours. The bed is changed frequently, the bed clothes are kept smooth, the mattress is either of the air or water variety. The need for evacuation of the bowel is best met by enemas. The bladder dysfunction is variously dealt with by repeated catheterization, indwelling catheter, cystostomy and tidal drainage, the last being perhaps the best. It is worthwhile to mention and to caution against the use of too hot water bottles in these patients whose perception of heat and cold is interfered with. Physical therapy of course is in order as soon as acute discomfort has subsided.

Infectious polyneuritis, in which an acute infection very often precedes the onset of signs of peripheral nerve involvement, also must be considered in the symptomatic treatment group. Here may be seen an associated facial palsy either unilateral or bilateral together with an increase in spinal fluid protein without a corresponding increase in cells. Fever therapy using typhoid vaccine intravenously in ascending doses has been employed by some. Large doses of the vitamin B complex, particularly thiamine hydrochloride are also recommended. More recently the employment of prostigmine has been suggested.

Herpes zoster in which the infection is in the sensory root ganglia deserves mention. Not only is the acute pain unbearable at times but unfortunately it may also be followed by a most distressing postherpetic neuralgia. There are several measures available in addition to anodynes. Some suggest repeated vaccination with small-pox vaccine every fifth day until a response is obtained. Still another means of attack is by the injection of 5,000 units of diphtheria antitoxin every other day for one, two or three injections. Thiamine hydrochloride in doses of at least 100 mg. intramuscularly daily may be beneficial also. Finally, a recent suggestion is that the corresponding sympathetic ganglia be injected with procaine 1 per cent. Excellent results have been reported with this.

Chorea. Perhaps a neurologist should not have the temerity to mention an acute infection in which the nervous system is concerned, but which involves other parts of the body as well. Chorea in the rheumatic complex is the condition referred to. While there is disagreement on this, I feel one should certainly consider fever therapy. It appreciably reduces the time of hospitalization although it must be admitted that in some cases with more or less severe cardiac involvement it is contraindicated. Under such circumstances isolation with shades drawn, no visitors and sufficient sedation four or five times per day should be the program.

Acute anterior poliomyelitis just about completes the nonbacterial group, at least for the purposes of this

discussion. Once again one is dealing with a controversial subject. The concept of muscle spasm, incoordination and alienation has stirred up much discussion to say the least. The physician as a consequence hardly dares to treat a patient with this disease without the employment of hot packs and the remainder of the nonfixation technic. While it is difficult to see how treatment of the muscles can influence the progress of disease in the spinal cord it must be admitted that early movement employed in this plan is a step forward, and is better than the older fixation treatment which at times resulted in ankylosis and contractures. The two drugs recommended here, curare and prostigmine, have their champions and their antagonists. At the present perhaps the weight of opinion is against either being of any real value in poliomyelitis.

Brain Abscess. Passing over into the bacterial group of acute infections of the nervous system one must consider brain abscess, sinus thrombosis and meningitis. Brain abscess when the diagnosis is made requires surgical interference. It takes about three weeks for an adequate capsule to form around the abscess so that great haste for surgical interference is not imperative if the case is observed from the beginning. On the other hand a ruptured abscess is very likely to be fatal, if it is not always so. Along with the surgical drainage one must not forget the sulfones and penicillin since their addition has resulted in much better management of brain abscesses. Sinus thrombosis calls for the same drugs and again, if it is evident and accessible, the focus must be surgically drained.

Meningitis. When we come to the meningitides we approach the acute infections of the nervous system, which now in many instances can be overcome. It is not too long ago that the mortality rates in all but the epidemic type were practically 100 per cent and even there it approached 60 per cent. Now excellent results may be expected in meningococcus meningitis by the use of sulfadiazine alone. In the average case 4 Gm. is given by mouth as the initial dose and this is followed by 1 to 2 Gm. every four hours keeping the blood level around 15 mg. per cent. After the temperature has returned to normal a level of 10 mg. per cent should be maintained for at least a week longer. A negative spinal fluid culture, a low cell count with predominately lymphocytes and a nearly normal sugar and protein are additional justifications for stopping treatment. All through this the patient should receive from 2,500 to 3,500 cc. of fluid per 24 hours and with each dose of sulfadiazine an equivalent amount of alkali should be given. A spinal puncture is necessary only for diagnosis in the beginning and for comparison at the end with perhaps another one in between. It should be emphasized that too high a dosage is better than too low a one. If the patient is comatose when first seen 5 Gm. of sodium sulfadiazine should be given intravenously in 1,000 to 1,500 cc. of physiologic salt solution. If necessary half this dose is given by the same route every 12 hours until the oral route can be adopted. A patient with overwhelming infection may also be given 200,000 units of penicillin intramuscularly immediately. Occasionally it may be necessary to give 10,000 units of penicillin in 10 to 20 cc. of saline at the time of the original lumbar puncture with repeated doses daily as may be necessary. The usual supportive measures such as sedation, blood transfusion and so on may be used as needed.

Pneumococcal, staphylococcal and streptococcal meningitis call for strenuous measures. In the first group doses ranging from 50,000 to 200,000 units of penicillin intramuscularly every three hours for two weeks, plus penicillin intraspinally one or two times daily for one week and enough sulfadiazine to keep the blood level at 15 mg. per cent are indicated. With the latter two groups the penicillin intramuscularly can be reduced to 40,000 to 100,000 units per dose. The intraspinal dosage in all of these is the subject of some controversy, as is the justification and necessity for the use of this mode of administration.

In considering the latter it is necessary to weigh the good against the bad. Among the reasons why some are cautious in using this mode of injection is the occasional occurrence of convulsions. Other complications include adhesive arachnoiditis, radiculitis, myelopathy and encephalopathy. It appears that in keeping the strength of the solution of penicillin down to 1,000 units per cubic centimeter and keeping the total individual dose down to 20,000 units or less the danger of these untoward reactions is reduced to a minimum. Other factors active in this consideration are the frequency of injection and the duration of the intraspinal therapy. It is worthy of note that the giving of 500,000 units intrathecally was reported recently. The patient developed a series of convulsions but recovered. The use of heparin intraspinally has been suggested to help in avoiding these side effects.

Inflammation of the meninges as the result of Hemophilus influenzae infection has been treated with streptomycin alone and with good results. This is particularly of interest because previously this type, which is seen primarily in children, carried with it a mortality of 90 per cent or more. The dose is still to be determined but at present 0.8 to 1.0 Gm. daily are given in divided doses every three hours intramuscu-

larly with 100 to 175 mg. dissolved in each cubic centimeter. At the same time an initial dose of 50 to 100 mg. dissolved in 5 to 10 cc. of saline may be given intrathecally followed every 24 hours by 25 mg. or more depending on the course of the disease. The intraspinal therapy usually may be stopped after a week, whereas the intramuscular injections may have to be continued for seven to ten days longer. It may be necessary and wise to supplement the above with a sulfone and to continue this for some time after cure. In very severe cases as judged by the clinical state of the patient and the spinal fluid sugar level, type specific rabbit antiserum may be employed.

In using streptomycin it must be kept in mind that it is toxic to the eighth nerve resulting in vertigo and deafness. Renal damage also is possible. If it is not effective in three days a change in treatment regime should be made. While using it the susceptibility of the organism to it should be determined if possible.

Of greatest interest insofar as streptomycin is concerned is its possible beneficial effect in meningeal invasion by the tubercle bacillus. The outcome in these cases has been uniformly fatal but there is reason to be hopeful that this may change. Patients with undoubted tuberculosis of the meninges have improved and are still alive six and more months after the diagnosis has been made. This alone is a step forward. However, this may be temporary and cases have come to autopsy in which the meningitis has disappeared but intracerebral tuberculomas are found. A suggested intrathecal dosage is 100 to 200 mg. every 24 to 48 hours for two to six weeks. The solution is made up with 100 to 200 mg. in 1 to 5 cc. of saline or spinal fluid. 2 to 3 Gm. daily in four or six doses may be given intramuscularly, for as long as six months. The solution is made up with from 100 to 250 mg. per cubic centimeter of saline or sterile water.

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WHAT'S YOUR DIAGNOSIS?

A 40-year-old man was admitted to the Medical Service on February 26, 1940 and died on March 23, 1940. About three months before admission he developed a cough of gradually increasing severity. It was productive of large quantities of mucoid sputum but no blood or pus. Shortly after this he noted marked fatigability and then weakness which became progressively worse. Three weeks after the onset of the cough he walked six miles to see a doctor who gave him medicine for his cough. While walking back home he noticed that his feet and ankles were swelling. Following this the edema progressed to involve the entire lower extremities. Two months before admission he was forced to go to bed. A physician prescribed tincture of digitalis, 12 drops three times daily. He took this regularly until admission. During the first week in bed he also took magnesium sulfate daily. The edema decreased but did not disappear. During the illness there had been mild dyspnea but no orthopnea nor paroxysmal nocturnal dyspnea. Several times immediately after or during an attack of coughing he had a "throbbing" pain in the left anterior chest associated with a feeling of oppression beneath the sternum in the lower portion. For years he had been known to have palpitation with tachycardia and frequent skipping of beats.

He did not believe that he had had fever, but frequent drenching night sweats had occurred. There had been no chills, rash or joint pains. He had lost about ten pounds in weight. His appetite had decreased somewhat but there had been no nausea, vomiting, or jaundice. Nocturia occurred twice per night with pain and burning on urination. Oliguria developed a short time before he was admitted.

There was no known history of rheumatic fever, tuberculosis, or syphilis.

Physical Examination. Temperature 99.6° F.; pulse 110; respiration 26; blood pressure 115/60. He appeared chronically ill. He coughed frequently during the examination, producing mucoid sputum. The skin was warm and moist with numerous wheals scattered over the trunk. A few questionable petechiae were noted. The lymph nodes were generally palpable except in the cervical region. They were discreet

Case protocol given third- and fourth-year students for the clinicopathologic conference, Vanderbilt University School of Medicine, Nashville, Tenn.

and nontender. The eyes were normal except for two small hemorrhagic spots in the right lower conjunctival sac. The left ear-drum was perforated and a small amount of pus was present in the left auditory canal. Many of the teeth were missing and the gums were infected. The thyroid gland was not enlarged. The carotid artery pulsations were overactive. There was dullness with suppressed breath sounds and fine inspiratory râles at the left base. The heart was markedly enlarged to percussion, both to the right and left. It was overactive, rapid and the sounds were loud. A loud, long, rough systolic murmur was present at the apex. This was transmitted to the base with decreasing intensity. A soft, blowing diastolic murmur along the left sternal border was described by one observer. The pulmonary second and mitral first sounds were both accentuated. The peripheral arteries were thickened and tortuous. The abdomen was soft. The liver was palpable one fingerbreadth below the costal margin, was firm and nontender. The spleen was palpable about two fingersbreadth below the costal margin. There was slight tenderness in the left costovertebral angle. No other abdominal masses were felt. Genitalia and rectum were normal. There was moderate pitting edema of the ankles. The nailbeds were somewhat cyanotic and there was suggestive early clubbing of the fingers. No abnormal neurologic signs were present.

LABORATORY DATA

Urine: (15 specimens) Sp. gr. 1.014–1.025; albumin 1 + to negative; sugar negative. Many RBC occurred in some specimens, in others few RBC and casts. Urine culture: Plate—sterile; Broth—streptococci and bacilli.

Blood	RBC	WBC	Hgb.
Feb. 26	3,450,000	7,400	9.1
March 11	3,980,000		9.0
March 19	2,980,000	6,750	8.6

Differential Count (Feb. 26): Seg. 79%; Eos. 2%; Bas. 1%; Lymph. 17%; Blasts. 1%.

Kahn Test: Negative.

Nonprotein Nitrogen: Feb. 27—32 mg.%; March 2—31 mg.%; March 5—50 mg.%; March 9—52 mg.%; March 15—33 mg.%.

Total Serum Protein (Feb. 29): 4.93 Gm.%; albumin 2.60 Gm.%; globulin 2.33 Gm.%.

Cholesterol: 122 mg.

Blood cultures were positive, for Streptococcus viridans on Feb. 28, Feb. 29, March 5, March 8, March 12, March 16 and March 19.

PSP: 55% and 70% excretion in two hours.

Sputum stained for acid-fast organisms (Feb. 28): Negative.

Stools (Feb. 29): Positive for occult blood.

Chest X-Ray (Feb. 27): Heart markedly enlarged.

Electrocardiogram (Feb. 27): Rate 115, PR 0.18, R_4 absent. T inverted in precordial leads. Sinus tachycardia. Record suggested myocardial disease.

March 7: Rate 85, PR 0.18 0.20. Sinus rhythm. Record within normal limits.

March 22: Rate 130–140. PR 0.18 low voltage lead 3; QRS slurred 1, 2, 3. ST 1, 2, 3 depressed. R_4 absent; W-shaped QRS_4. Numerous premature beats from various foci. Record suggested acute myocardial injury, possibly infarction.

Venous Pressure: 200 mm.

Vital Capacity: 1,700 cc.

Hospital Course. During the 4-week hospital course there was an irregular, spiking febrile course. The patient was digitalized with disappearance of the edema, fall in venous pressure, increase in vital capacity and decrease in pulse rate. Sulfanilamide 0.9 Gm. every four hours and soda bicarbonate 4 Gm. three times daily were administered. After four days this was discontinued and sulfapyridine 1 Gm. every four hours was given. During the second week he was improved; the temperature remained normal for several days and thereafter remained relatively low. Numerous small whole blood transfusions were administered. Nausea occurred as a result of sulfapyridine. Blood cultures remained positive. The edema recurred during the third hospital week. Several showers of petechiae were noted.

On March 22 after complaining of generalized abdominal aching for several days the patient suddenly became dyspneic, orthopneic and cyanotic and the generalized abdominal pain became worse. He coughed up blood-tinged sputum. Râles were noted at the right base. A gallop rhythm was present. Following this episode he grew progressively worse. He became very dyspneic and more orthopneic with tachycardia (160). There were frequent extrasystoles and a gallop rhythm. The liver became larger and tender. The temperature rose to 103°, râles increased at the lung bases and he died on March 23.

(For diagnosis see page 286)

The diagnosis of hypothyroidism in the absence of frank myxedema undoubtedly is often overlooked. This paper calls attention to the suggestive clinical features of this state. Also it emphasizes that thyroid gland therapy is not without danger at times.

Adult Hypothyroidism

Observations Based on a Study of 151 Cases, with Detailed Reports of Two Typical Cases*

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Hypometabolic states are probably encountered more frequently than is usually appreciated.[1,2] The most important of these states, which may mask under a variety of clinical pictures or occur in association with other conditions, is hypometabolism due to deficiency of the thyroid hormone. Hypothyroidism is especially important because it is readily amenable to replacement therapy.

This report, based upon a study of the case records of patients with hypothyroidism admitted to a large hospital during a period of eleven years, may serve to emphasize certain points which are important in the recognition and treatment of hypothyroidism. Two illustrative cases, one of classical myxedema with the usual dramatic result of treatment, the other that of a patient to whom harm may possibly have been done by overtreatment, are included in the report.

Incidence. During the years 1935 to 1945 inclusive 151 cases of hypothyroidism were recognized on the wards of the Charity Hospital, but of these only about one-third had frank or classical myxedema. Undoubtedly some cases escaped recognition, and it is certain that a much larger number of cases were seen in the outpatient department, the records of which we have not studied. About three-fourths of the cases occurred in women. The incidence was highest in the third decade of life; in 40 per cent of the cases symptoms appeared before the age of 30. In a similar series of 50 cases studied by Kohlhas[3] the average age was 34 years. Although about half of the patients admitted to the hospital are Negroes, only a fourth of the patients with hypothyroidism were of the colored race.

Etiology. Most of our cases appeared to be instances of primary hypothyroidism, that is, cases in which the thyroid gland itself was primarily at fault. In only two cases was the hypothyroid state secondary to pituitary deficiency, or associated with serious hypofunction of other endocrine glands. Again, most of our cases were idiopathic, in that the deficiency of thyroid secretion could not be attributed to organic disease of the thyroid gland due to known causes. Eight cases occurred following thyroidectomy, but in none was there evidence of previous thyroiditis, or of syphilis, tuberculosis, carcinoma, or amyloidosis of the thyroid gland. Associated diseases, the symptoms of which contributed importantly to the clinical picture, existed in about 50 per cent of the cases, the most frequent concomitant conditions being gynecologic disorders and gallbladder disease. Hypometabolic states may be the result of therapeutic use of such drugs as thiourea and its derivatives, iodine, and the newer radioactive isotopes. Many excellent classifications of hypothyroidism based on etiologic factors may be found in the literature.[4-6]

Clinical Picture. In our series only the patients with frank myxedema presented the complaints usually considered to be typical of hypothyroidism, and even in these patients typical symptoms were often elicited only by careful questioning of the patient or a relative after the physician had suspected hypothyroidism because of the patient's appearance. It appears that patients with hypothyroidism either have few or no subjective complaints, or complaints which of themselves may suggest disease of some other organ or organ system, or which seem to indicate a psychosomatic disorder. The largest single group in our series complained of gynecologic disorders: menstrual disturbances, hot flushes, low abdominal pains, and amenorrhea. Men in a similar category complained of impotence and loss of libido. Others complained of gastro-intestinal symptoms: nausea, vomiting, epi-

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gastric fullness, flatulence, eructations, constipation, even diarrhea. Still others had aches and pains suggestive of arthritis or neuralgia or myositis. Some complained of dyspnea, palpitation, or pain in the chest, so that heart disease was suspected. Many of the patients presented symptoms which in no way differed from those of psychoneurotic individuals without metabolic disorder. Other authors have noted similar findings.[7-9] Occasionally a case of hypothyroidism clinically appeared to be actually in a state of hyperthyroidism such as Rose [9] has described as "paradoxical hypothyroidism."

Questioning, however, elicited more characteristic symptoms in most of the patients: Such symptoms as diminished tolerance to cold and increased tolerance to heat, diminished perspiration, dryness of the skin, increasing scantiness of the hair, progressive lack of energy, and increasing absent-mindedness.

Physical Signs. The patients with frank myxedema all presented characteristic physical signs, but it should be noted that in several instances the diagnosis escaped one or more observers. In some, the observer mistook the facies of myxedema for that of chronic nephritis or pernicious anemia, or considered the patient merely to have an expressionless face. It is interesting also that several patients in whom myxedema was suspected from their general appearance were found not to have any metabolic disorder.

In the patients with myxedema, the face seemed expressionless, the eyelids puffy. The skin was pale, often slightly yellowish, and dry, thick and cool. The lips and tongue were large, the voice coarse. The hands and feet were often swollen, but pitting did not occur on pressure. The hair was dry and scanty, the eyebrows thin. Most of the patients were not noticeably obese, though many had gained weight; none was very fat, and some were actually thin. Usually the heart rate was slow, the blood pressure normal or low; a few patients had concomitant hypertension. Cardiac enlargement was present in some of the cases.

In the milder cases, however, the characteristic facies was not observed, the patients often appeared alert, sometimes even hyperkinetic. Slowing of the mental processes was not apparent in many of the patients. In this group the principal signs which aroused suspicion were dryness and coolness of the skin and scantiness of the hair.

Laboratory Data. In all of our patients with frank myxedema the basal metabolic rate before treatment was below minus 20 per cent Occasionally the BMR was below this level in patients with milder manifestations of hypothyroidism. However, in 12 of the cases proved by response to therapy to be actual cases of hypothyroidism the initial basal metabolic rate was within the lower limit of normal (— 10).

Determinations of serum cholesterol was made only in the more recent cases. In our series the serum cholesterol level was capricious and often did not correlate with the basal metabolic rate, physical signs, and response to therapy, but this may well be due to errors of technic in the determinations. Certainly in the majority of cases of hypothyroidism, the serum cholesterol level is above 200 mg./100 cc.[10, 11]

Anemia of more than slight degree (hemoglobin below 10 Gm.) was present in 40 per cent of our cases. In the patients with myxedema on whom electrocardiograms were taken, the complexes of the ECG were usually low, but this was not the case in most of the patients with milder degrees of hypothyroidism.

Diagnosis. As stated earlier, the diagnosis in most cases was first suspected because of physical signs; the presence of these signs led to careful questioning which in some cases brought to light characteristic subjective symptoms. In all the cases of frank myxedema and in most of the milder cases, it was possible to confirm the suspected diagnosis by two or more determinations of the basal metabolic rate, but in the milder cases the diagnosis could be made with certainty only after a definitely favorable response to therapy was observed.

Complications. Among the 151 patients there were 38 who had other diseases as well as hypothyroidism, the most frequent being gynecologic disorders, cholecystitis, nephritis, tuberculosis, and diabetes mellitus. Most of the other conditions, however, were concomitant diseases and not specific complications of the hypothyroid state. A rather small percentage of the patients had heart disease, but we cannot be sure of the number in which the heart trouble was related to the hypothyroidism and in how many it was coincidental.

Treatment. The patients in this series were treated on different services of the hospital and were thus under the supervision of several physicians. Many more physicians were concerned in the details of the therapy. In many cases the patients returned to private physicians after their discharge from the hospital, so that a long term follow-up was not possible. Therefore, only a general statement can be made regarding the therapy employed and its effects. In general, the treatment consisted of the administration of thyroid substance by mouth in small dosage, and of measures directed toward the control of concomitant disease.[18] In general the results of therapy were excellent. Results were most striking in the patients with classical myxedema, most of whom were restored

to normal health. Improvement in the milder cases, though less striking, was just as definite. There were, however, patients in whom definite objective improvement was noted who continued to have subjective complaints. This suggests that in some patients with hypothyroidism, many of the subjective symptoms are of psychoneurotic origin and not specifically correlated with the hypometabolic state.

Discussion. For the most part, the results of our study serve merely to emphasize facts about hypothyroidism which have been established by earlier surveys. The important facts to be emphasized are as follows:

1. The subjective complaints in most patients do not suggest the diagnosis, and perhaps in many cases are of psychogenic origin or due to concomitant disease and not specifically correlated with the hypometabolic state.

2. Classical signs of myxedema are present in only about 30 per cent of the cases.

3. In mild cases, the diagnosis can be established with certainty only by the response to treatment. The basal metabolic rate may be low in normal individuals and within normal limits in persons with definite hypothyroidism.[12]

4. Large doses of thyroid substance are not needed to correct the hypothyroid state and are in fact dangerous. Dosage in excess of 180 mg. (grains iii) daily is rarely if ever indicated, and the initial daily dose should not exceed 30 mg. (grain ss). On this dosage nearly all patients who really are hypothyroid will manifest improvement within two weeks. The dose of thyroid substance should not be increased at intervals of less than three to four weeks.[13-16] Angina pectoris or even true myocardial infarction may occur as a result of overenthusiastic treatment.[17]

CASE REPORTS

CASE 1. Mrs. V. R., white housewife and farm worker, 23 years of age, was admitted to the hospital with the chief complaints of weakness, dizziness, and general body aches and pains. Her present illness began four years ago during the first trimester of her first pregnancy. She first noticed generalized body aches and pains with no static location. With the passage of time her symptoms increased in number and intensity. She began feeling weak, listless, tired during both the day and night with constant muscle and joint pains not relieved by salicylates. Mild exertion would cause spells of dizziness, and ringing in the ears was noticed often. She stated that she had gained 30 pounds in weight over the four-year period. Since the birth of her baby, the patient had been obstipated. Inconstant bouts of epigastric distress with gaseous eructations accompanied by sharp epigastric pains radiating over the precordium were also experienced. During the four-year period she required a larger amount of clothing than previously during the winter months; the arrival of summer brought some relief from her troubles. In the six-month period prior to admission a number of new complaints were experienced by the patient. She first noticed blurring of vision and spots in front of her eyes when reading. Also in this latter period her gums felt sore and bled easily and her teeth felt loose. Her family told her during this time that her skin was turning a lemon yellow color and she had noticed that her face, eyelids, arms and legs were thick and puffy during this same time. Occasional bouts of nonproductive cough were also present. She stated that her tongue felt so thick that it seemed to fill her entire mouth and her speech was slurred and syrupy. She continued to menstruate normally. Her family and past history were noncontributory.

On physical examination the patient was found to be a well developed, well nourished, white female who appeared chronically ill. She was not obese. The hair was thick, coarse, and straight but not thin. Her skin appeared lemon yellow tinted with deeper brown irregularly splotched patches covering portions of her face. She appeared listless and her face was without expression. Her respirations were noted as 10 per minute with a very slow expiratory phase. Blood pressure was 84/54. The pulse rate was 70, its rhythm regular. Her general hair distribution appeared normal, and subcutaneous fat was evenly distributed. The eyelids were puffy and soft. The lips were somewhat thicker than normal. The tongue was shiny, smooth, red and symmetrically enlarged to almost twice normal size. The thyroid gland was not palpable. The heart, lungs, and abdomen were essentially negative to examination. Rectal and vaginal examinations did not add any further positive data. There was moderate, equal symmetrical nonpitting swelling of both ankles.

Laboratory Data. An ECG taken on admission showed a prolonged PR interval (0.21 sec.) and low T waves. The stool was negative for ova, parasites, and cysts. Blood Wassermann was negative. A hemogram revealed a hematocrit of 30 mm. (Wintrobe); hemoglobin of 12.5 Gm.; RBC of 4.05 millions; WBC of 4,950 with a differential count of 72 lymphocytes, and 28 neutrophils. Urine was normal.

Blood chemistry revealed glucose of 110 mg., serum protein of 7.55 with an A/G ratio of 1.62/1; cephalin

flocculation test was negative and the icteric index was 6.0. Serum cholesterols, recorded at weekly intervals, were 172, 178, and 185 mg. A gastro-intestinal x-ray series showed a normal configuration of the esophagus, stomach and duodenum. Two BMR's determined on consecutive days were — 25 and — 34 per cent.



FIG. 1. Case 2. (*Left*) Before treatment. (*Right*) After six weeks of replacement therapy.

Desiccated thyroid 30 mg. daily was begun three weeks after admission to the hospital. A BMR taken the day before therapy was begun was — 35. One week later the BMR was — 28. She was discharged to the outpatient clinic one week after treatment was begun. A BMR taken one month after hospital discharge was found to be — 14. The patient felt in her own words, "like a new woman." Since discharge she had been taking 60 mg. of desiccated thyroid substance daily. Her facial and ankle edema had entirely disappeared, and the pulse rate had increased to 84. On her last visit to the clinic two months after discharge from the ward, the BMR was still — 14. The patient stated that she had never felt better. On this visit the blood pressure was 90/60, pulse rate 88. An ECG made at this time showed an increase in the amplitude of the T waves. The patient was then discharged to her local physician on a daily dose of 60 mg. of thyroid substance.

CASE 2. Mrs. I. K., a 33-year-old white housewife, was admitted to the hospital with the chief complaints of nausea, vomiting, precordial and epigastric pains. The patient stated that her troubles began about three months prior to her admission. She awoke one night feeling "deathly ill," weak and dizzy and on arising from bed she became nauseated and vomited. During the following day the nausea and vomiting persisted, but gradually subsided in a few days. A period of one week then elapsed during which time she remained relatively free of symptoms. This period was followed by a repetition of the previous symptoms. No jaundice, diarrhea, acholic stools, or change in urine color was noted by the patient. Vague precordial and epigastric pains followed the second attack and became more marked in the week previous to admission. She described the pains as sharp, knifelike and localized and made worse on deep inspiration. A gradual loss of appetite took place during the course of this illness, but no appreciable weight loss was noted. The patient said that she felt nervous, easily upset, and overwrought with anxiety as to the nature of her illness. During this period she stated that her vision began to blur, and she noted that her eyelids were getting puffy. In the three-month period prior to admission she noticed vague body pains which were most marked in the lower portion of the back. She sometimes slept 18 hours a day and often awoke feeling quite tired. Her memory seemed to be failing; she said that she could not remember where she had put things. For several months she had noted swelling of the ankles, which persisted overnight. She had visited a number of beauty salons during the past year in search of a cure for roughness, dryness, and scaliness of the skin, but without success.

Bilateral salpingo-oophorectomy and subtotal hysterectomy had been performed on the patient when she was 19. A positive Wassermann had been discovered at this time, and she was given a long course of antiluetic therapy. A year before admission she had received a course of liver injections for an anemia and "run down condition." One of her sisters was receiving pneumothorax treatments for tuberculosis.

On physical examination the patient was found to be well developed and well nourished; she appeared chronically ill. The facial expression appeared blank and masklike (Fig. 1A). The skin was coarse, dry, scaly and somewhat thicker than normal. The axillae and pubic regions were hairless, but the scalp was covered with abundant coarse dry red hair; the hair was loose, strands being easily removed by moderate traction. She was not obese, height being 66½ inches and weight 148 pounds. Blood pressure was 90/70, pulse rate 60. The neck veins were not distended. The tongue was rounded and considerably thicker, and the lips were enlarged. The thyroid gland was not palpable. The patient's breasts, heart, lungs and abdomen were essentially negative to examination except for the presence of an old lower midline abdominal scar. Vaginal examination revealed a tiny urethral orifice found on the distal portion of the anterior

vaginal wall. The vaginal introitus admitted only one finger. The cervix was small but presented no lesions. A small, firm, nontender mass was noted in the left adnexal region. Rectal examination was essentially negative. There was noted soft nonpitting edema of both feet and ankles. Neurologic examination was negative.

A rather extensive laboratory workup was performed in this patient's case in order to rule out possible gastro-intestinal pathology as well as a possible pituitary deficiency. Gastro-intestinal x-ray series revealed a normal esophagus, stomach and duodenum. Cholecystogram showed a normal functioning gallbladder with no evidence of stones. Blood Wassermann was negative. A cerebrospinal survey showed normal dynamics, a pressure of 100 mm. of water, a negative Pandy test and a protein of 62 mg. with a negative Wasserman and colloidal gold curve. A lateral x-ray of the skull showed a normal sella turcica and no evidence of intracranial pathology. Stool examinations were negative. A hematologic survey revealed: 12.5 Gm. of hemoglobin; 2.68 millions RBC; 5,700 WBC with 60 per cent neutrophils and 40 per cent lymphocytes. A hematocrit of 31 mm. (Wintrobe) was obtained on admission. Urine was normal. Urine urobilinogen excretion levels were within normal levels on two occasions. A resume of the blood chemical studies obtained are as follows: Glucose tolerance curve showed 95 mg. per cent fasting, 129 mg. per cent one half hour, 133 mg. per cent one hour, 114 mg. per cent two hours, and 77 mg. per cent in three hours. Cholesterol levels at weekly intervals prior to replacement therapy were 276, 332, and 434 mg. per cent. Total serum proteins were 6.85 with an A/G ratio of 1.12/1. Blood urea nitrogen was 16.0 mg. per cent. Icteric index was 10.5; cephalin flocculation test was negative. An ECG taken previous to thyroid therapy (Fig. 2A) showed low voltage QRS complexes. BMR's prior to therapy were — 32, — 25, — 35, and — 35 per cent respectively.

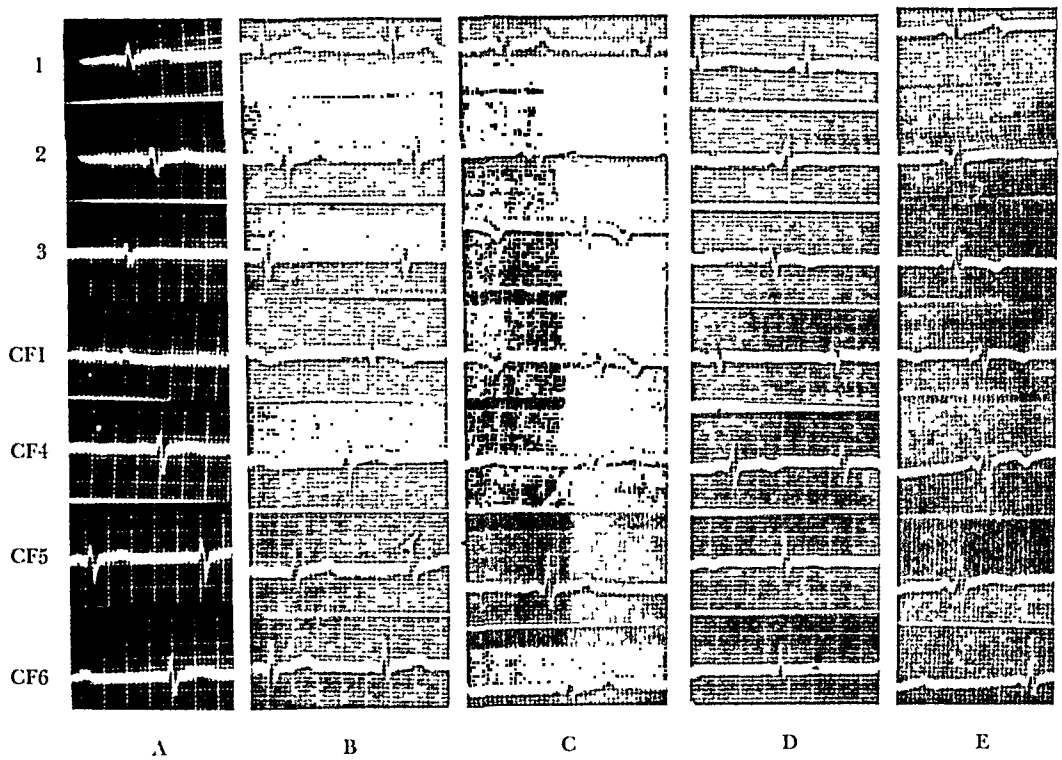


FIG. 2. Case 2. (A) Electrocardiogram before treatment. (B) After three weeks of replacement therapy. Note increase in the height of the T waves. (C) After twelve weeks of therapy. Note the low T waves in lead 2, and the sharp inversion in lead 3. The patient had not complained of pain in the chest. (D) Four weeks later, after an episode of chest pain. The ECG is essentially unchanged from (C). (E) After six months of therapy. The inversion of the T waves in lead 3 is less marked.

Treatment was begun with 30 mg. of thyroid substance daily. After two weeks the dose was increased to 60 mg. She was also given 1 mg. of stilbesterol daily, multivitamin capsules, and ferrous sulfate. A

BMR made three weeks after therapy was begun was — 21 per cent. The patient was then discharged from the hospital and followed in the outpatient clinic.

The patient was again seen one months after discharge and stated that she felt very well. The pulse rate was 68 on this visit, and no ankle edema was seen. The patient's facial features had returned to normal (Fig. 1B) and the tongue seemed somewhat thinner and the skin less scaly. An electrocardiogram made at this time showed no abnormal changes (Fig. 2B). At this visit the daily thyroid dosage was increased to 120 mg. daily.

Twelve weeks after the beginning of treatment the patient was seen again. On this occasion she seemed in low spirits and complained of general body aches. Her previous medications were continued, and the dose of thyroid substance increased to 180 mg. daily. An electrocardiogram made immediately after this visit (Fig. 2C) showed sharp inversion of the T waves in lead 3, suggestive of changes in the diaphragmatic wall of the left ventricle. The patient was reached and advised to reduce the thyroid dosage to 60 mg. daily.

The patient was rehospitalized two weeks later because of severe pains in her ankles and knees and because of a feverish sensation. At this time she stated that five days prior to this admission she noticed sharp pains under the left border of the sternum on mild exertion. On arising from bed the next morning she became nauseated and vomited. The pain in the chest was made much worse by the retching, and now radiated up the left side of the neck and behind the left ear. Within 24 hours it had spread to an area under the left breast and to the region of the left scapula. The pain disappeared after a few days. Physical examination was noncontributory. An x-ray of the chest was negative for lung pathology, and the urinalysis and hemogram were within normal limits. The ECG was unchanged from the one recorded two weeks previously.

The patient was discharged after six days in the hospital, and has since been followed in the outpatient clinic, where she is seen at intervals of four to six weeks. All of the objective signs of hypothyroidism have disappeared; her facial appearance is normal, the most recent BMR was — 14 per cent, hemoglobin 14 Gm., erythrocyte count 4 million. The electrocardiogram (Fig. 2D & E) shows less marked inversion of the T waves in lead 3. However, she still has numerous subjective complaints: dizziness, arthralgia, and bouts of nausea and vomiting—which we believe are psychogenic in origin. It is highly likely that this patient sustained a coronary occlusion, and it is probable that its occurrence was related to overdosage with thyroid hormone. For this patient 60 mg. daily has proved to be an adequate daily dose.

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The author reviews the several causes of esophageal obstruction, emphasizing especially the treatment of cardiospasm.

Treatment of Esophageal Obstruction*

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Dysphagia is the chief symptom of esophageal obstruction and the usual thing which brings the patient for relief. When one cannot even eat in comfort he is indeed miserable; gratitude for relief is commensurate with the previous suffering.

Treatment, which must start with an accurate diagnosis, will not be considered at this time, since the choice of methods is dependent upon the type of obstruction. The various conditions producing dysphagia will be considered and relative space given in the order of their frequency.

CARDIOSPASM

Cardiospasm, also called achalasia, preventriculosis and idiopathic dilatation of the esophagus, is the most common cause of difficulty or inability to pass food from the mouth to the stomach. It is comparable to anal spasm, and regardless of the original cause (this is not known) habit is the greatest factor in its continuance.

The obstruction varies from a slight lag at the cardia and a feeling of pressure, to increased discomfort with inability to make food enter the stomach, and finally a marked stretching of the esophagus with decompensation. At this time there is regurgitation of the food, either on swallowing or at night, and the patient is thoroughly miserable (Fig. 1, 2, 3).

One would suppose after the writings of Myers, Plummer, Vinson, and others that treatment would be well standardized and universally known. However, it is irritating to those of experience to know that there seems to be shown an almost complete ignorance of the subject in most books, articles, and in our medical schools.

Just as in anal spasm, no sedatives or antispasmodics have any effect. There is no medical treatment for real cardiospasm. It is not only useless, but denies the patient the immediate cure to which he is entitled. These patients are definitely not psychoneurotic and often are not even nervous.

On the other hand surgery is usually not indicated. Various operations from gastrostomy to the formidable esophagogastrostomy have been done. Except in the rarest case operation is not only unnecessary, but is hazardous and unjustifiable. To do a big operation for a condition which is easily curable in five minutes is comparable to using ice tongs to pick up a lump of sugar.

Mechanical overstretching of the cardia by water pressure is the only cure for real cardiospasm. It is sure, spectacularly quick, and relatively safe in expert hands. It is, in fact, probably the most remarkable therapy in medicine or surgery.

Occasional cases may be cured by air dilators, mercury bags, and even by bouginage, but usually all these prove inadequate and often, by irritating, make the condition worse. The only reliable method of overstretching is by the Plummer hydrostatic dilator. It is portable, but there is often difficulty in making proper connections for temporary use and it is much more satisfactorily used in a permanent office setup.

The dilator consists of a semistiff shaft on the inside of a tube the size of a stomach tube, with a metal bougie at the tip, which can be threaded on a guide, to be described later. The tube communicates with a rubber bag which is covered with a silk bag to maintain the sausage shape on dilating, and this in turn is covered by another rubber bag to facilitate passing down the esophagus. The other end of the tube communicates with a Y tube, one arm of which goes to the water faucet with a pressure gauge interposed, and the other arm to the exhaust pipe to release pressure (Fig. 4).

A thread guide is always necessary for any esophageal instrumentation. Without it the esophagus may be perforated, but with it one may use the necessary force to push the dilator through the spasm. On the day before treatment nine to twelve feet of coarse button-hole twist are swallowed slowly, at a rate of about eight inches an hour. Early the next morning six or eight more feet must be swallowed. The slow swallowing in two portions is necessary in order that the thread will find its way through the cardia, stom-

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FIG. 1. Mrs. P., referred for dysphagia. Third degree cardiospasm, cholecystitis and diabetes; 24-hour retention. One treatment cured her and resulted in a 20-pound gain in weight.

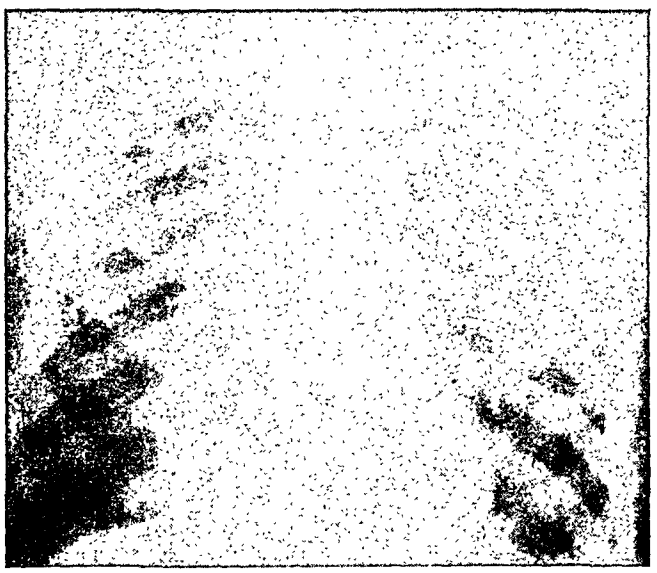
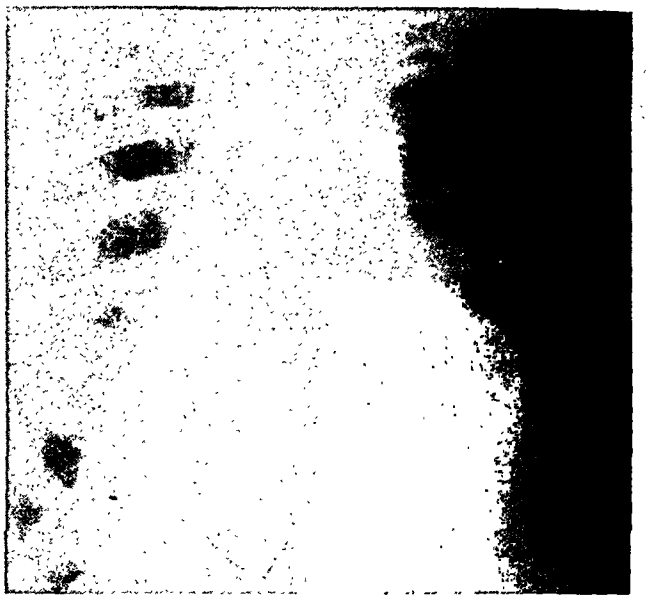


FIG. 2. P., a colored patient, showed fluid level in the esophagus, appearing at first glance to be pericardial effusion. Two dilatations were necessary to cure this patient. (One patient described in the literature was tapped for supposed fluid in the pleural cavity.)



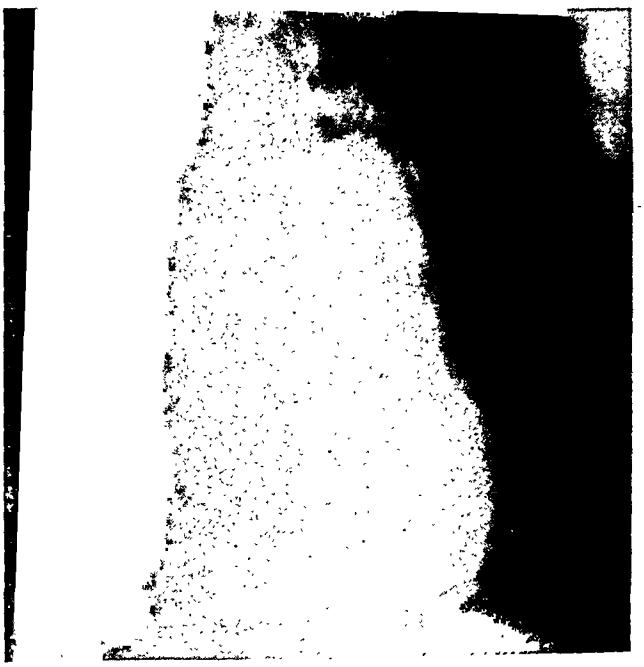


FIG. 3. (*Top*) Roentgenologic study shows silhouette apparently of cardiac enlargement. (*Bottom*) With change of position the dilated esophagus is revealed as part of the shadow. (Patient cured by dilatation.)

ach and pylorus, and the upper loops of bowel without knots. If a tangle should occur in the first section it is passed through and the second section will be smooth. The swallowing of the thread is the hardest part of the procedure but eventually the tightest constriction will be passed. If a knot should be found at the first trial about eight more feet may be tied to the end of the thread and swallowed until the following day.

The thread guide must be taut so that it cannot be pulled up. Before passing the Plummer bag we often pass the bougie down the thread into the stomach to be sure that there are no knots. One hand holds the thread guide taut while the other pushes the bougie on it down the esophagus, through the cardia, and into the stomach. In the very rarest case there is such marked angulation of the esophagus that it is impossible to pass any instrument and in all cases there is

danger of perforation if any force is used without the guide.

Anesthesia, even local, is usually not necessary and general anesthesia cannot be used as the pain sense must be present. A barbiturate may be given one hour before treatment and in a very sensitive patient the hypopharynx may be anesthetized by a 1 per cent pontocaine solution.

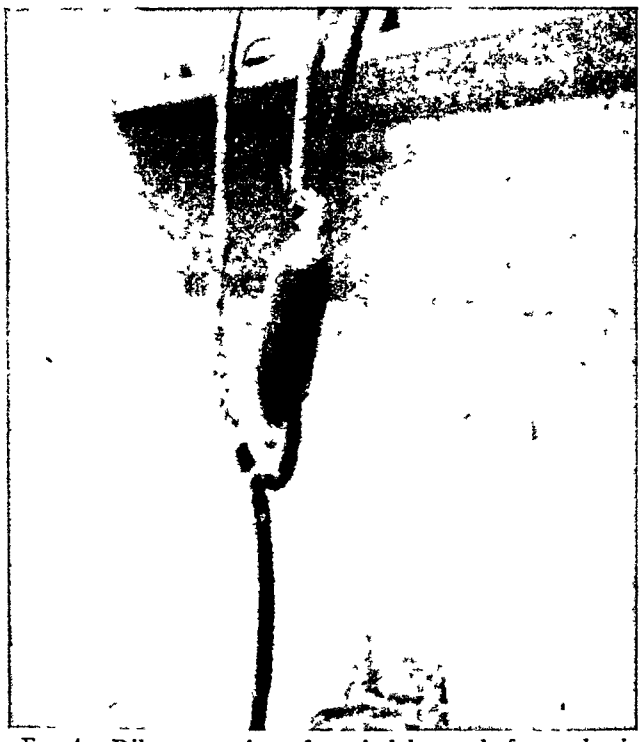


FIG. 4. Dilator consists of a whalebone shaft on the inside of tube with small metal tip to thread on guide. Tube communicates with rubber bag which is covered by sausage-shaped silk bag to keep the shape and then by another rubber bag.

The tip of the Plummer dilator is threaded on the guide. The patient is in the upright position with the head back to nearly an esophagoscopic position. The instrument is helped over the base of the tongue and over the epiglottis by the finger, after which it is rapidly passed into the cardia, 44 cm. from the teeth.

During the passage the thread guide must be kept taut by one hand while the other hand pushes the instrument down. When the tip meets the block at the cardia, the experienced operator knows from the feel whether he is dealing with a cancer instead of a spasm. This is one reason why the esophagoscope is rarely indicated before treatment. Spasm has a yielding feel, while an organic block feels like a stone wall. In my experience x-ray and instrumentation have been far more successful diagnostically than esophagoscopy and biopsy. The patient can be cured of his cardiospasm in much shorter time and with less discomfort than the esophagoscopy would have taken. Even if the block is found to be cancer it is proper to dilate mildly if the instrument has passed through, even though metal dilators would have been the choice.

When the dilator is in place, the water pressure is gradually turned on with one eye on the gauge and the other on the patient's hand, which he has been instructed to raise if there is real pain. It is unsafe to dilate beyond the point of onset of pain. If there is no pain, pressure is gradually raised to about 22 feet. At this point the bag is distended to about 1.5 inches in diameter and is very hard.

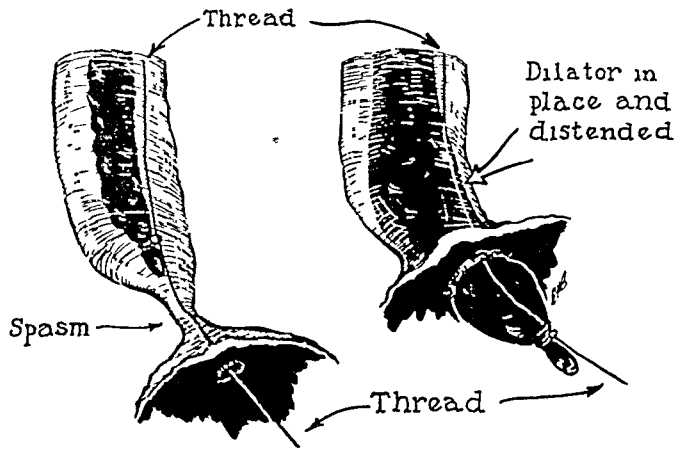


FIG. 5. The Plummer dilator is shown (*left*) being passed down to the cardiospasm and (*right*) it is being distended to relieve the spasm.

As the pressure is raised there is a distinct tug on the instrument as if it were being drawn into the stomach and it is necessary to hold it firmly at the teeth. This is one of the sensations that leads the operator to know that the dilatation is progressing satisfactorily. One can also feel the heart beat against the instrument.

After the maximum dilatation has been obtained, the pressure is released. The instrument is then moved on about one inch and the pressure again raised to make doubly sure that the pressure was exerted in the right place, although since the bag is so long there is little chance it would not be in the cardia. The water is then allowed to escape, the instrument withdrawn, and the thread cut off and swallowed.

Judgment must be used in dilating. Insufficient pressure will fail to cure, and too much could rupture the esophagus. Certain factors are necessary for safety and success. The diagnosis must be accurate. No instrumentation should be attempted without the string guide being properly in place. Lastly, real pain should never be disregarded.

Some conditions to be ruled out before attempting dilatation are: mediastinal tumor, hiatal hernia, cancer of the cardiac end of the stomach, anurysm, diverticulum, foreign bodies, and other more rare entities.

Very rarely the esophagus is so angulated and distended that it is impossible to get the semiflexible shaft around the corner, even with the guide. In one such case I had to dilate in retrograde fashion through a gastrostomy opening. The patient completely recovered and the gastrostomy was allowed to close.

With hydrodilatation the results are immediate and the procedure takes less than five minutes. There is no hospitalization, no anesthesia, and everything is finished at one session, since one successful dilatation is permanent and final in 75 per cent of the cases. The procedure is always an ordeal, but well worth it. There may be occasional shock. Rupture and perforation are possibilities, but are usually preventable. Angina and coronary thrombosis can occur and my first death was due to a coronary closure. The mortality should not exceed 3 per cent, and my own has been only a fraction of 1 per cent.

In a successful case the patient is immediately cured and can at once eat a regular meal in comfort. It is true that the patient may be a bit hysterical, may have slight shock, and some sore throat, but when it is all over so soon and the patient is well, why should anyone be subjected to inadequate dilatation by other methods or be treated with antispasmodics which never help? Finally, why should one be subjected to a serious operation?

As has been said, every patient who is successfully dilated will have immediate relief. About three-fourths will never have a return, but in some the habit will not have been broken and the procedure will have to be repeated. Our series is one of the largest in the world, due to the fact that our original instrument was one of the first east of the Mayo Clinic, and for some years we drew patients from Maine to Mexico. Six hundred and twenty-two cases have been studied. All were not dilated, as some were quite mild. There were 233 spasms of the cardia, 238 grade 1 cardiospasm, 97 second stage and 54 third stage. Some were a bit difficult to classify.

Of the first stage cases, 86 per cent were dilated once and 14 per cent twice with a cure of 85.8 per cent and 14.2 per cent unimproved. Of second stage cases 83 per cent were dilated once and 17 per cent twice with 75 per cent permanent cures. Of the third stage cases 50 per cent were dilated once, 26 per cent twice, and 24 per cent more than twice. Of these (third stage), 94 per cent had satisfactory results and only 6 per cent were unimproved. It is seen, therefore, that about 85 per cent of all cases obtained satisfactory results and that the most severe had the best results.

The fact that the highest percentage of cures appeared in the worst cases is also seen in other conditions such as gallbladder operations. It is perhaps explained by the fact that the worst cases are so thoroughly miserable that the improvement is more apparent. The unimproved ones can be explained by (1) the presence of some other condition, (2) refusal of the patient to co-operate or continue treatment, and (3) possibly some fault in technic, since theoretically cure should be obtainable in 100 per cent.

ESOPHAGOSPASM

Spasm of the esophagus above the cardia presents a very difficult problem and is quite resistant to any form of treatment. Fortunately it is fairly rare. Esophagospasm may occur as a generalized spasm which seems to be often a part of a general spasmophilia. The entire esophagus may be spastic or spasms may be localized at different levels. Some form of dilatation may be used but is usually unsatisfactory. This type of dysphagia is, however, possibly more influenced by medical treatment than is cardiospasm.

CARCINOMA OF THE ESOPHAGUS

Resection of cancer of the esophagus is being attempted more and more with increasingly fewer operative deaths. Actual cures are still so rare that the outlook is most discouraging. However, when metastases are not known to be present it is worth trying, since there is no other chance for cure, and even an operative death is probably preferable to the death from such a condition.

When obstruction is known to be due to inoperable cancer, we have our choice of two methods of palliative treatment; gastrostomy, or dilatation of the stricture by increasing sizes of metal bougies, preceded by a flexible spiral tip, passed on the silk guide.

Some years ago I strongly advocated gastrostomy, reasonably early. Then Dr. Porter Vinson won me over to the dilatation method by stating that the patients could be kept swallowing reasonably well until death, by an occasional dilatation. Of late I have swung back to gastrostomy as a preference. At times I employ both methods.

Vinson states that gastrostomy has a mortality of from 10 per cent to 50 per cent. I cannot understand this as my own mortality is practically nil. He also states that removal of irritation of food passing over the growth does not slow its progress, and this is defi-

nitely not my experience as I have had some cases improve so much and for so long as to throw some doubt on the diagnosis.

If dilatation is decided upon it is usually possible to carry it out since given enough time the thread will find its way through the finest stricture and after the thread is in place any stricture can be dilated. After dilatation various types of tubes have been used to maintain the opening. I have not had experience with these, but am led to believe that they are rarely satisfactory.

Roentgen treatment or radium are so ineffectual in cancer of the esophagus that their use is not advised.

CICATRICIAL STRICTURE OF THE ESOPHAGUS

Stricture following ingestion of lye, or other caustics, is not as common as it was a few years ago. In this type of obstruction, metal bougie dilatation is also indicated and it is but rarely that gastrostomy is necessary. If gastrostomy has been done, then retrograde dilatation with rubber bougies can be done. Also, if a gastrostomy is present, a thread guide may be swallowed by mouth, brought out of the gastrostomy wound, and tied to the mouth end making a circle. Metal dilators can be fastened to the guide and the whole thread pulled from the mouth, through the stricture and out the gastrostomy, or in reverse if easier.

In the past it has always been recommended to await full development of a stricture before dilating, but recently very early passage of bougies has been advocated, shortly after the ingestion of the corrosive.

ESOPHAGITIS

It has been said that nonspecific inflammation of the esophagus is one of the most common lesions of the esophagus, but it is quite rare in my experience as compared to either cardiospasm or carcinoma. When dysphagia is present or where there has been bleeding from ulceration dilatation with metal bougies is indicated.

FOREIGN BODIES

Esophageal obstruction caused by solid foreign bodies such as coins, pins, etc., has been publicized so thoroughly that the treatment is well known. Occasionally a cardiospasm or other partial obstruction is converted into a complete block by a food bolus which cannot go either way. In one of these cases a plug of meat was removed by passing a stomach tube, making suction against the meat, and pulling the bolus up. In another case the lower esophagus was so packed that the mass had to be removed in small fragments by forceps through the esophagoscope.

Of late it has been recommended that the bolus be digested by repeated instillation of small amounts of 5 per cent Papain solution. I have had success in the one case in which it was tried.

PARA-ESOPHAGEAL OR HIATAL HERNIA

Many hiatal hernias are symptomless and these do not require treatment, even if quite large. This is one reason why they are placed here in a position of relative unimportance. When these hernias do give symptoms, however, they are most important. Whenever pain or dysphagia is present to any degree treatment is indicated.

The dysphagia may often be cured by the passage of a large (60 French) bougie into the stomach. Palliative measures consist in having the patient take small meals, avoid conditions which raise intra-abdominal pressure, and having him sit in a partial upright position at night.

If these measures fail, surgery is indicated. It consists in reduction of the para-esophageal hernia, narrowing of the opening in the diaphragm, with possibly some fixation of the stomach below the diaphragm. The operation is done by an approach either below or above the diaphragm but is probably done better through the thorax.

ESOPHAGEAL SHORTENING

The abnormally short esophagus with part of the cardiac end of the stomach above the diaphragm is less common than hiatal hernia but more serious in that it is more prone to produce continuous or alarming symptoms. It is subject to frequent ulceration and hemorrhages, either gross, or hidden, with anemia as the common symptom. There is not infrequently a stricture occurring at the esophagogastric junction.

Even in the presence of ulceration and hemorrhage, bouginage is necessary to relieve the dysphagia as well as to permit curing of the ulcer. Cure of the ulcer is not apt to occur as long as there is stagnation.

One of my patients had not taken solid food during his life. Any attempt to do so since a child had been followed by pain and vomiting or regurgitation. Marked cicatrization had occurred and there was an ulcer the size of a fingernail demonstrated by x-ray study on the second occasion. At the first x-ray examination diagnosis had been made of simple congenital stricture. Treatment with the smaller size bougies produced immediate improvement in symptoms and

he had eaten much more than ever before. Passage of the larger size caused a hemorrhage sufficient to necessitate hospitalization and transfusion. However, he is now able to eat in comfort and I believe that the ulcer has been healed.

Surgery is not as satisfactory in this type of herniation and the approach is preferably abdominal. Attempt is made to free the lower esophagus and draw the stomach down below the diaphragm and to fix it in this position.

PLUMMER–VINSON SYNDROME

The Plummer-Vinson syndrome is at times called hysterical dysphagia but it can hardly be entirely a manifestation of hysteria since organic changes of anemia, glossitis, and enlarged spleen often with achlorhydria may be present.

There is no actual obstruction present and yet the treatment of the dysphagia consists in passing a large size olive, after which relief is obtained, and symptomatic treatment for the other complaints may follow.

SUMMARY

In conclusion, it may be said that all patients with an esophageal obstruction should be dilated, in one way or another. There are definite indications for the choice of methods. Cardiospasm requires hydrostatic overstretching. All other obstructions are treated by either olive bougies or metal cylinder sounds. Above all, no instrumentation should ever be attempted without the thread guide.

The Parkwood Medical Building

BOOK REVIEWS

DISEASES OF METABOLISM. By Garfield G. Duncan, M.D. Second Edition. 1,045 pages, 163 illustrations or graphs. Philadelphia, Saunders, 1947. $12.00.

The readers who have found the first edition of this book so helpful will welcome this second edition. Dr. Duncan has selected 20 collaborators, each of whom is an authority on the subject he has covered for this volume.

The book has as its objective the presentation of the abnormalities of metabolism. So much of the knowledge in this field is of such highly technical nature that it is too complex for the average practitioner. Yet, as in all scientific fields, some fundamental knowledge is essential if one wishes to apply the principles in some practical fashion. Thus the practitioner of medicine in treating or managing metabolic disturbances should have some of the biochemical and physiologic fundamentals in mind. The collection of writings appearing in this book provides the bridge between the research and laboratory study on the one hand and the practical management of disorders of metabolism on the other.

The introductory chapter defines metabolism, heat and energy production, nutritional requirements, basal metabolism and the like. In the following four chapters there are discussions of the metabolism of carbohydrates, proteins, fats and minerals respectively. Here are presented the normal processes of metabolism of these substances and the abnormalities in disease. Water balance in health and disease as reflected in the interrelationship of water and electrolytes is considered thoroughly in a readable manner.

In the chapter on the metabolic aspects of blood disorders, the production and destruction of blood cells is considered, as well as iron metabolism. A lengthy chapter is given over to the biochemistry of the vitamins and their place in the human economy. The deficiency diseases are described and their management as well. Chapters follow on undernutrition and obesity.

Next follow discussions of the subjects of xanthomatoses, glycogen disease, porphyria, cystinuria and other rare disturbances of metabolism. There is an excellent discussion of gout. The sections on hyperinsulinism and diabetes mellitus are most complete, not only in the presentation of the fundamental knowledge but also in the practical treatment of these diseases.

The second edition includes new chapters on diseases of the thyroid gland and of the kidney.

The sections as listed above have appended to them, extensive bibliographies.

(Continued on Page 278)

Poorly controlled diabetes mellitus carries with it the dangers of certain complications requiring surgical intervention. The authors emphasize the prophylaxis in terms of adequate diabetic management as well as the serious nature of these complications.

Medical Control of Diabetes in the Surgical Patient

WILLIAM W. SHAPIRO, M.D. AND HUGO O. FENSKE, M.D.

CHICAGO, ILLINOIS

Diabetic treatment, in general, aims at the maintenance of a state of well-being in which the life and health of the individual will not be jeopardized by intercurrent infection, acidosis will be avoided, and complicating degenerative disease will be prevented. It is not only necessary to maintain the well-being of an individual from day to day, but also to control him so that he will be as healthy as possible at a future date. The critical and all-important problem in diabetes is to maintain such control that, years later, serious degenerative disease will be avoided.

When a patient asks us why we are insistent in our demands, why frequent observation and changes in dosage of insulin are made, especially when he is feeling well, we emphasize that while his present good health is a very desirable feature, he must remain healthy today so that his health will be unimpaired ten to twenty and more years hence. While he is concerned perhaps only with his sense of well-being today, the years will pass rapidly, and if ten or twenty years later he is confronted with progressive loss of vision, gangrene, or a flagging heart, his awakening will be quite rude. Rarely, among intelligent patients, will there be a failure of co-operation. Patients who do not co-operate are our controls.

In private practice, the incidence of severe degenerative disease among patients who accept good care is exceedingly low. In them the need for major operative procedures to arrest degenerative processes is insignificant. In consultation practice, we see many who have not received good care. These patients have a high incidence of surgical complications.

Approximately 3,500 patients with surgical complications, usually severe, were seen from 1938 to 1947 at the Cook County Hospital. Twenty-five per cent of these were unaware that they were diabetic prior to the onset of the complications that necessitated admission to the hospital. They had previously considered themselves in good health, and many of them did not learn that they had diabetes until they were in the hospital. A history of polydypsia, polyuria, previous ill-health, and weight loss was not obtained. Their complaints, on admission, included severe infectious processes, and often a moderate or marked gangrene necessitating high amputation. Many of them commented on their previous good health, and adequate wound healing. From them we noted, and it is a common experience, that gangrene or visual disturbance might be included as initial symptoms in the diabetes of the older individuals.

A large number of our surgical cases had received inadequate medical care for many years because of our failure to invoke their co-operation. In these patients, the morbidity and mortality was very high. We believe that the idea of permitting patients to have a hyperglycemia originated entirely from the failure of getting patients to control themselves adequately with insulin. These individuals could not be induced to accept management. Since they got along comfortably for many years, but not too many, with hyperglycemia and without developing signs of degenerative disease some credence was given to the point of view that perhaps this was another good way of treating diabetes. They looked well, felt well, had hyperglycemia, glycosuria and never acidosis. In our experience, however, the patients who refused rigid control, ultimately developed very serious degenerative complications.

The only finding common to all of our severe surgical diabetics was hyperglycemia with or without glycosuria. Renal threshold for glucose higher than 200 to 300 mg. per cent was present in about 20 per cent of the patients.

Unfortunately, both from the point of view of teaching physicians who would learn how to manage diabetes, as well as for the good care of the diabetic, there has been a tendency to pay little attention to people who have hyperglycemia accompanied by slight or no glycosuria. In fact, many clinicians have taught and still teach that such people are not diabetic. These patients, usually old, often have severe degenerative conditions. In them there is little tendency towards acidosis even if insulin is not used. That diabetes of the old is relatively mild and requires little care has been a prevalent notion. Obviously, blindness, heart infarction and gangrenous legs are never mild conditions. They are all definitely a part of diabetes of the aged, as well as a part of diabetes of long duration.

All of the above discussion leads to two inescapable thoughts. First, in all diabetics having degenerative processes there is only one constant finding—this is hyperglycemia. Second, the greatest need in the treatment of diabetic degenerative disease is good control of the diabetes at its onset, so as to prevent the degenerative conditions, if possible.

Much evidence has been produced which suggests that adequate diabetic control and probable prevention of degeneration can be obtained by avoidance of hyperglycemia.[1] We heartily concur in these views. The experiences with our patients represent fine evidence in support of this concept. Diabetics in whom a diagnosis is made early, and in whom the blood sugar is kept close to normal levels are not as prone to develop gangrene and blindness as the others. People who may have had hyperglycemia for some time with insignificant glycosuria and no other symptoms frequently show far advanced degenerative conditions. Children whose diabetes is well controlled at the outset without too many fluctuations in their blood sugar level, grow well, attain good physiques, have few complications, and for many years have shown no visible degenerative conditions.

We do not know whether prolonged hyperglycemia produces degenerative arterial disease. However, we are sure that the mechanism in the adequately nourished, nonobese individual which is associated with the maintenance of blood sugars at normal levels without too many fluctuations will prevent or delay arteriosclerotic degeneration. It is, perhaps, too much to hope that the control of the hyperglycemia alone is the factor that will prevent severe arteriosclerosis. Pursuing the idea that hyperglycemia is in some way tied up with the development of delayed sequelae, we believe that it should be combated regardless of the age of the patient and regardless of whether there is a heavy, moderate or absent glycosuria.

The discussion thus far does not seem to have much bearing on the medical management of the surgical diabetic. However, one must bear in mind that one of the most serious problems in the diabetic is that of surgical treatment of arteriosclerotic limbs which have become gangrenous, with or without accompanying infection. In this group of individuals the mortality is extremely high. Thus one will come to realize how important and worthwhile adequate prophylactic care can be in preventing or delaying these most unfortunate sequelae.

We have taken statistics from our surgical diabetic service during the two years 1943 and 1945. While there was no particular reason for selecting these two years, it will be seen that the figures coincide to a remarkable degree for both years. In 1943, there were 313 patients admitted to the service, and in 1945 there were 316. Among these patients there were 65 deaths in 1943 and 65 in 1945. Seventy lower extremity amputations were performed in 1943 and 77 in 1945. Thus, in 147 amputees, there were fifty deaths, a 34 per cent mortality rate (Tables 1 and 2).

TABLE 1

Age by Decades for All Amputees (1943)

	Diabetics		Nondiabetics	
Age	Deaths	Total	Deaths	Total
10's	—	—	—	1
20's	—	—	—	1
30's	—	—	—	6
40's	—	5	2	10
50's	7	21	2	21
60's	13	31	6	16
70's	4	12	9	25
80's	—	—	3	6
90's	1	1	1	4
	—	—	—	—
Total	25	70	23	90

TABLE 2

Age by Decades for All Amputees (1945)

	Diabetics		Nondiabetics	
Age	Deaths	Total	Deaths	Total
10's	—	—	—	1
20's	—	—	—	2
30's	—	1	1	5
40's	—	7	4	11
50's	5	21	—	10
60's	9	29	8	31
70's	7	15	4	27
80's	2	2	3	5
90's(?)	2	2	—	1
	—	—	—	—
Total	25	77	20	93

There were 78 deaths for both years among the patients who did not have amputations. This amounted to a 16 per cent mortality (Tables 3 and 4).

TABLE 3

Age by Decades of Diabetic Patients Not Having Amputation (1943)

AGE	DEATHS	TOTAL
10's	1	8
20's	1	12
30's	—	7
40's	6	43
50's	5	72
60's	12	65
70's	16	32
80's	1	4
90's	—	—
	—	—
	40	243

DEATH AND CASE TOTALS

40 + 25 = 65 total deaths
243 + 70 = 313 total cases on service

TABLE 4

Age by Decades of Diabetic Patients Not Having Amputation (1945)

AGE	DEATHS	TOTAL
10's	—	4
20's	—	8
30's	1	13
40's	2	25
50's	10	87
60's	12	69
70's	11	28
80's	1	4
90's(?)	1	1
	—	—
	38	239

DEATHS AND CASE TOTALS

25 + 38 = 63 total deaths
239 + 77 = 316 total cases on service

The total number of deaths, including amputees and nonamputees, was 128. The per cent mortality for the whole service, therefore, was 20.3. One in five patients who entered the service died (Tables 5 and 6).

Of the nonamputees in the fourth decade, there were 68 patients with eight deaths, 12 per cent. In the fifth decade there were 159 patients with 15 deaths, 9.5 per cent. In the sixth decade, there were 134 patients with 24 deaths, 18 per cent. In the seventh decade, there were 60 patients with 27 deaths, 45 per cent. In the eighth decade, there were eight patients with two deaths, 25 per cent.

Of the amputees, in the fourth decade, there were 12 patients with no deaths. In the fifth decade, there were 42 patients with 12 deaths, 28.6 per cent. In the sixth decade, there were 60 patients with 22 deaths, 36.7 per cent. In the seventh decade, there were 27 patients with 11 deaths, 40.8 per cent.

There were 24 toe amputations performed with five deaths (Tables 7 and 8).

Of the 147 amputees, there were 62 women and 85 men. The mortality rate for the women, with 24 deaths, was 38.7 per cent. The mortality rate in the men, with 26 deaths, was 30.6 per cent (Tables 7 and 8).

TABLE 5

Mortality Rates in 1943

Total mortality diabetic service	20.7%
Mortality for diabetic amputees	35.7
Mortality for nondiabetic amputees	25.5
Mortality in 6th decade, diabetic amputees	41.9
Mortality in 6th decade, nondiabetic amputees	37.5

TABLE 6

Mortality Rates in 1945

Total mortality diabetic service	19.9%
Mortality for diabetic amputees	32.4
Mortality for nondiabetic amputees	21.5
Mortality in 6th decade, diabetic amputees	34.4
Mortality in 6th decade, nondiabetic amputees	25.8

TABLE 7

Amputation Level for All Amputations (1943)

	DIABETICS		NONDIABETICS	
	DEATHS	TOTAL	DEATHS	TOTAL
Thigh	20	60	22	62
Lower extremity	2	2	—	8
Toes	3	8	1	20
	—	—	—	—
	25	70	23	90

Sex of All Amputees

	DIABETICS		NONDIABETICS	
	DEATHS	TOTAL	DEATHS	TOTAL
Male	15	45	14	72
Female	10	25	9	18
	—	—	—	—
	25	70	23	90

It is interesting to note that in the two years there were 183 amputations among the nondiabetics in the hospital, with 43 deaths, 23.5 per cent. Of the nondiabetic amputees in the sixth decade, there were 43 patients, with 14 deaths, 25 per cent. Among the diabetic amputees in the sixth and seventh decades, the mortality rate was 36.7 per cent and 40.8 per cent respectively.

TABLE 8

Amputation Level for All Amputations (1945)

	Diabetics		Nondiabetics	
	Deaths	Total	Deaths	Total
Thigh	23	59	20	75
Lower extremity	—	2	—	4
Toes	2	16	—	14
	25	77	20	93

Sex of Amputees

	Diabetics		Nondiabetics	
	Deaths	Total	Deaths	Total
Male	11	40	17	78
Female	14	37	3	15
	25	77	20	93

The average age of death on the entire service was 65 years. At first glance, it would seem that the mortality rate among the amputees was particularly high, but there may have been a number of factors contributing to these results.

The greater number of our patients is drawn from the unenlightened masses of the city. They have been people who are incapable of taking care of their diabetes, both as to insulin and diet therapy. Most of them have been self-appointed espousers of the idea that as long as one felt well and there was no acidosis, insulin therapy was unneeded. Many of them have visited a physician only on payday night for insulin injections. Others have received extensive and unwarranted physiotherapy, and the condition of many of the patients on admission was pitiable. Many of the patients procrastinated in having surgical treatment. Sometimes, after a patient had persistently refused surgery and then relented, the condition was too far advanced for successful treatment. In many instances, we have had "relative trouble." It is surprising that many children are reluctant to have a parent's leg amputated because of the possibility that the parent might recover and prove a burden to them.

Our difficulties are illustrated by a female patient about 50 years of age whom we had been treating intermittently for many years. This patient, for some unexplainable reason, required 400 to 500 units of insulin daily. She refused to maintain a rigid control. About six months before her death, she developed a destructive osteitis of the right os calcis. The heel became a bag of pus. For weeks she required an amputation but persistently refused surgery. She was now on a maintenance dose of between 500 and 700 units of insulin daily. She finally agreed to amputation, providing we would allow her to return home to arrange her affairs. We never saw her again. About four days later, we received a call from a house physician at an outlying hospital who stated that this women had been brought to his hospital in diabetic coma and that her physician had mustered up enough courage to give her 200 units of insulin. When this dose had been unsuccessful, the patient was given up as hopeless. The patient quickly succumbed. We informed the physician of this patient's usual insulin requirement and politely suggested that some multiple of the given dose might have been more successful.

An exceedingly important factor in evaluating the statistics in our series of patients is that we have a very serious social service problem, more serious in fact than we are frequently able to cope with. We find it easy to get patients in the hospital and onto our service, but it is sometimes very difficult to get them out, especially if they are minus a leg. They all have homes when they enter the hospital, but after the amputations, the homes somehow seem to disappear. Consequently, a large number of our patients remain in the hospital an unnecessary length of time. This length of time is frequently long enough to permit death from other conditions unassociated with the surgical condition.

We have analyzed the causes of death on the service for 1943 and 1945. These are listed in Tables 9 and 10.

TABLE 9

Causes of Death on Surgical Diabetic Service (1943)

Intestinal obstruction due to incarcerated hernia	1
Uremia due to renal failure	1
Coronary occlusion	5
Diabetic acidosis	4
Bronchopneumonia	6
Arteriosclerotic heart disease	7
Septicemia due to cellulitis	3
Streptococcal septicemia	1
Staphlococcal septicemia	1
Septicemia—type undetermined	3
Hypoglycemia	1
Cerebral hemorrhage	2
Cerebral thrombosis	1
Cerebral embolism	1
Cardiac decompensation	3
Gas gangrene	2
Lung abscess	1
Hemorrhage due to duodenal ulcer	1
Diabetic gangrene	8
Gastric hemorrhage	1
Anaemia of undetermined origin	1
Dilatation of the heart	1
Lobar pneumonia	1
Unclassified	9

Average age of death on the service—65.5 years

TABLE 10

Causes of Death on Surgical Diabetic Service (1945)

Intestinal obstruction	2
Uremia due to renal failure	2
Coronary occlusion	6
Diabetic acidosis	6
Chronic myocarditis with decompensation	1
Bronchopneumonia	11
Arteriosclerotic heart disease	10
Acute appendicitis	1
Septicemia due to infected burn	1
Septicemia due to cellulitis	4
Anesthetic death	1
Squamous cell carcinoma of ant. triangle of neck	1
Hypoglycemia	2
Diabetic gangrene	8
Cerebral hemorrhage	1
Urinary retention due to hypertrophied prostate	1
Lobar pneumonia	1
Pulmonary embolism	1
Hemolytic streptococcal septicemia	1
Unclassified	2

Average age of death on service—64.4 years

It will be noted that many of the causes listed are only remotely connected with the peripheral vascular complication. However, if the patient previously had had an amputation during his stay in the hospital, he was listed as an amputation death. It will be noted, also, that there were 32 cardiac deaths, a mortality rate in all of the deaths of about 25 per cent. These mortality figures do not compare too favorably with those of other institutions.[2, 3]

The medical preparation of our patients for surgery is quite simple. In a hospital as large as Cook County Hospital, there must be some sort of a routine employed so that all of the resident physicians and internes will think of the management of the diabetic in about the same manner. Most patients are given a diet that is basal for their needs. We have found that such a diet is satisfactory when it consists of 120 Gm. of carbohydrate, 70 Gm. of fat, and 60 Gm. of protein. Since most of the patients have a high fasting blood sugar and these all receive protamine zinc insulin, a small night feeding is given in addition. This feeding consists of milk and six small soda crackers. Whenever feasible, children are given a diet as near optimal as possible. Patients with thyrotoxicosis are provided pre-operatively with a diet high in protein and carbohydrate containing adequate calories based on their increased basal metabolic requirement, plus additional food to about 30 per cent above their basal requirement. This is to provide for gain in weight and strength.

When the special physical disturbances of the patient such as severe hepatitis, chronic protein deficiencies or avitaminoses are present, time permitting before surgery, special supplementaries of the needed substances are given. The routine dietary management of the severely ill diabetic with surgical complications, who has anorexia, severe ketosis, and inability to eat a well rounded meal because of mental haziness, is that of milk alone in a daily dose of two liters. This is usually given in amounts of 500 cc. four times a day, or 400 cc. five times a day. Orange juice is added frequently as a supplementary feeding in daily quantity of about 600 cc. The latter is used especially when the feeding problem is difficult, as in individuals in whom there is marked liver glycogen depletion, and it is desirable to have an increased glucose intake. Liquid protein supplements are given as needed.

The two liters of milk furnish an average intake of carbohydrate 100 Gm., protein 60 Gm. and fat 80 Gm. This yields 1,360 calories and is isocaloric with the diet previously listed. The 600 cc. of orange juice adds 60 Gm. of carbohydrate to make a total of 160 Gm. of carbohydrate, 60 Gm. of protein and 80 Gm. of fat. This simple plan of management has proved satisfactory and adequate for many years.

Nearly every patient has a high fasting blood sugar level, and is controlled most satisfactorily by protamine zinc insulin plus supplementary injections of unmodified insulin given at desirable intervals. Blood sugar determinations are made as needed. We also maintain a rigid urinalysis routine. The specimens are collected as fasting and three hours after each meal. The hours of collection are usually 7 A.M., 11 A.M., 4 P.M., and 8 P.M. Only in serious diabetic emergencies, when a more complete check on the urine is desired, is there any modification of this procedure. Thus, when severe acidosis is present, the specimen taken three hours after eating is discarded. Another urine specimen is obtained one half to one hour later, and thus the static level of sugar and acid content is appraised and insulin administered accordingly.

Where surgery is contemplated, the patient is brought up to the morning of the operation on the same feeding schedule and insulin dosage. On the morning of the operation, insulin—protamine zinc, crystalline, or a combination of the two are given in exactly the same dosage as before. If the surgery is to be done under local anesthesia, and no subsequent gastric upset is expected, the usual feeding is given and the medical routine is uninterrupted. The operation is usually planned for a late hour in the morning.

When a general anesthetic is the one of choice, the usual insulin dose is given the morning of the operation. The insulin is given an hour or more before the usual time, and an intravenous feeding of 1,000 cc. of 5 per cent glucose is given very slowly. Immediately after the fluid is given, surgery is performed and then postoperatively another 1,000 cc. of 5 per cent glucose, either in distilled water or in normal saline, is given. We believe that with such a routine it is much easier to appraise the patient's diabetic status. This method of dietetic and insulin preparation is quite simple and has proved satisfactory for many years. We can recall no instance in elective surgery in which this type of procedure has fallen short or proved harmful to the patient.

In the presence of acute surgical emergencies, no attempt is made to get the patient completely controlled before correction of the surgical condition is done. Adequate and frequent doses of insulin are given along with normal saline solution, and in the presence of a rapidly dropping blood sugar level, satisfactory progress will be made.

In eye surgery, almost always an elective procedure, we think that the best results are obtained when the patient's blood sugar levels are maintained as closely as possible to normoglycemic levels, without too frequent fluctuations that may produce a hyperglycemia. With such preparation, the results of eye surgery in the diabetic have proved most satisfactory. In some institutions there is doubt as to the desirability of very rigid control of the blood sugar level in a diabetic who will have a cataract removed immediately. This point of view has not coincided with our experience.

Emphasis has not been adequately placed, we believe, on the fact that in a previously uncontrolled diabetic, especially an individual who has lost a great deal of weight, largely through water loss from the tissues, one of the immediate, noticeable effects of adequate insulin therapy is a fixation of water in the body. At first this fixation is largely extracellular and several weeks to a month must pass before these retained fluids become an integral part of the tissues. The eyes are very sensitive to this phenomenon. Thus, one of the earliest manifestations of beginning diabetic control is a blurring of vision. This blurring is associated with anatomic changes in the eye due to such a vicarious water retention. In three to four weeks after the onset of the treatment, the vision is restored to the normal of the particular individual. Perhaps it is unwise to do delicate surgery on human tissues under these circumstances, and insulin might best be avoided if immediate surgery in a diabetic who was previously uncontrolled, is required. However, we see no reason why, in an elective procedure, surgery cannot be delayed until control is good and the patient's health is restored to its optimum.

A similar problem exists in the continuing management of the elderly arteriosclerotic diabetic who has a high fasting blood sugar in the range of about 200 mg. per cent with little or perhaps no glycosuria. Shall this blood sugar be brought down to a normal level? In the hospital such approaches to normal levels, at the same time avoiding hypoglycemia, can be accomplished readily. In ambulatory patients such a feat is very difficult because with a high renal threshold the usual yardsticks are not apparent. Most of us agree that hyperglycemia is an evil, but some tend to condone such a condition in the older individual. We think that hyperglycemia is an evil and should be controlled at any age. We do not believe that the fact that surgical wounds will heal in the presence of hyperglycemia is a valid reason for permitting it to exist. Permitting hyperglycemia in these older patients is simply a corollary to the point of view that any hyperglycemia and glycosuria could be permitted under given circumstances. Hyperglycemias have been permitted in patients because of the fear of disaster that might be produced by hypoglycemia. This consists of the substitution of one undesirable feature for another. Hypoglycemias should and can be avoided at all times if the patient receives the care that he requires.

Immediately postoperatively, the patient's condition is checked by frequent routine urinalysis and occasional blood sugar examinations. If the pre-operative management was adequate, there need be little concern about the patient getting far out of control. Healing will occur despite hyperglycemia, but when this imbalance occurs it should be changed as quickly and safely as possible. Where the insulin given is protamine zinc alone or with crystalline insulin in the morning and there seems to be more than slight glycosuria postoperatively, small token doses of about ten units of crystalline zinc insulin are added to each intravenous feeding until the patient's condition becomes satisfactory.

Usually the postoperative condition will parallel the pre-operative diabetic state. On some rare occasions, following surgical procedures, the insulin dosage will have to be markedly increased. We recall one of our patients who had been well controlled on about 50 units of insulin a day, had a resection of a carcinoma of the descending colon with a colostomy. Immediately afterward his insulin requirement rose to 225 units a day despite an uneventful recovery. His insulin requirement dropped again to about 50 units over a period of two months. At this time the colos-

tomy was closed and the insulin requirement rose to the same level immediately postoperatively, and then subsequently dropped.

The usual postoperative picture, however, is such that a severe load has been removed from the individual. Infection and inflammation have been reduced. Gangrene, if present, has been removed. This invariably will entail a diminution of the insulin dosage. Sometimes the drop is an immediate one. On other occasions, a seemingly large amount of insulin will be required. Then after a protracted period, the insulin dosage must be decreased rapidly to avoid severe hypoglycemia. In fact, the postoperative insulin needs of a patient sometimes serve as a barometer of his physical condition. When, in the presence of high insulin requirements after an illness or after surgery, the insulin dosage must be lowered precipitately, it is usually safe to assume that the deleterious effects of the complicating disease have subsided. In the postoperative patient a constant vigil, both with urinalyses and blood sugar examinations, must be made so that both hyper- and hypoglycemia is avoided.

The diet of the postoperative patient is changed to meet the optimal needs of the patient for his particular physical needs in an ambulatory environment.

In a large hospital such as ours, all of the surgical diabetic patients should be grouped together. The patients should be seen in common rounds by both the attending internist and the surgeon. The surgeon should have a special interest in this type of work. All of the surgical lesions should be followed carefully by the medical as well as the surgical staff.

We again wish to emphasize the morbidity associated with surgery in the arteriosclerotic diabetic individual. While the mortality statistics compare unfavorably with published statistics, it is very likely that our results would not suffer much by comparison if the same criteria for clinical evaluation of the statistical data were used in all instances. Those who have treated many patients of this type and have shown marked improvement in their own results are possibly entitled to offer valid criticism. We shall attempt, if possible, to encourage those who are continuing this work so that better results will be obtained.

SUMMARY

A study was made of the surgical diabetic service in a large general hospital. The care, treatment, mortality, operative mortality, type of patient and causes of death were reviewed. Particular emphasis was given to amputation statistics.

CONCLUSIONS

1. The incidence of degenerative changes in diabetics entering this hospital is very high.
2. Physicians treating diabetics should strive for the early control of hyperglycemia.
3. Internist and surgeon should continue to co-operate and seek even closer co-operation in the treatment of the surgical diabetic.

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CASE REPORT - - -

Islet Cell Adenoma of the Pancreas*

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Although numerous cases of islet cell tumors of the pancreas have been reported without the syndrome of hypoglycemia, most interest in such tumors has centered on this special syndrome. Pappenheimer [1] in *4,010 consecutive autopsy cases found five islet cell* adenomas, of which four were incidental findings and one had clinical symptoms of hypoglycemia, giving an incidence of 20 per cent with clinical symptoms.

A majority of these tumors are of small size. Whipple and Franz [2] in a review listed 26 instances of adenoma without hypoglycemic symptoms in which the size was recorded, with an average greatest diameter of 1.7 cm. There are several notable exceptions to the small sized tumor. Cottalorda and Escarra [3] listed one 13 × 8 cm. in diameter and Lecompte [4] one 10 × 7 × 4 cm. The largest islet cell adenoma recorded is that reported by Brunschwig,[5] which was 15 × 13 × 10 cm., this one being associated with the clinical symptoms of hypoglycemia.

In their review of these tumors, Duff and Murray [6] state that they occur throughout the entire range of life. However, it is interesting that in the lower age groups (below 40) the tumors almost always are accompanied by hypoglycemic symptoms.

CASE. H. R., a 54-year-old college professor, was admitted to the Medical College of Virginia Hospital in October 1945 with a complaint of a mass in his upper abdomen. In June of that year, while rubbing his stomach, he had noticed a walnut-sized mass in the upper abdomen. He was certain that the mass had increased in size since that time. A local doctor was consulted who referred him to the Medical College Hospital, following the report of a negative cholecystogram. The patient had had no subjective symptoms with this mass, except that in the two weeks prior to admission he had been conscious of a fullness in the abdomen and had not been able to eat as much as previously. There had been no other gastro-intestinal symptoms: no jaundice, nausea, nor vomiting; bowel movements were normal without the passage of blood. *Genito-urinary symptoms were absent.* He had lost about 15 pounds the preceding spring, but had regained 5 pounds at the time of admission.

The patient had scarlet fever in 1903, during which time his left leg swelled to twice the normal size and has remained so since, without subjective symptoms or much incapacitation. In 1913 a ruptured appendix was removed followed by drainage and a long convalescence. A severe case of typhoid fever was survived in 1921. In 1935 his right leg swelled to twice the normal size within a few hours, without redness or pain. It has remained swollen since, without subjective symptoms. Septicemia developed in 1936 and he remained very ill with delirium and inflammatory arthritis for three weeks. During this illness both legs and the external genitalia swelled to above the hips, accompanied by redness and heat. A deforming arthritis of some joints, most marked in the right hand and wrist remained after the illness. Swelling of the legs and genitalia subsided, but a few months later the left testicle was removed because it had atrophied.

Physical examination revealed a well developed, fairly well nourished white male who appeared well. The temperature, pulse, and respirations were normal. The blood pressure was 110/90. There were no abnormal findings in the head and chest. Abdominal examination showed an old McBurney incisional scar with two stab wound drainage scars. The abdomen was flat without tenderness or spasm. In the right upper quadrant a firm, moveable, nontender, orange-sized mass was palpated. This moved with respiration. The liver edge could be felt just to the right of the mass as it descended on inspiration. Because of its close contact with the liver margin and because of its mobility, it was thought that the mass arose from the liver; probably a hepatoma. The scrotum had an operative scar in the midline and one testicle only could

* The author wishes to express his appreciation to Dr. I. A. Bigger, Chief of Surgery, Medical College of Virginia, for his permission to publish this case and for his assistance and advice, and to Dr. S. D. Wu, Department of Pathology, Medical College of Virginia, for assistance with the pathologic studies.

be palpated. Both legs were swollen from the groin down, the lower leg to twice normal size. The swelling was firm and pitted slightly on firm pressure. The legs were covered with thickened, scarred skin, tightly stretched. Rectal examination showed a normal prostate and no masses.

On admission, the urine was negative, RBC 4.1 million, hemoglobin 86 per cent, WBC 8,000 with 56 per cent polymorphonuclear neutrophiles, 9 per cent eosinophiles, 30 per cent lymphocytes, and 5 per cent monocytes. The total protein was 6.2 with 3.8 albumin and 2.4 globulin. The Kline test was negative. No blood sugar determination was done pre-operatively as pancreatic involvement was not suspected.



FIG. 1. Lobulated masses of tumor cells, separated by fibroni septa. (Hematoxylin and eosin × 72.)

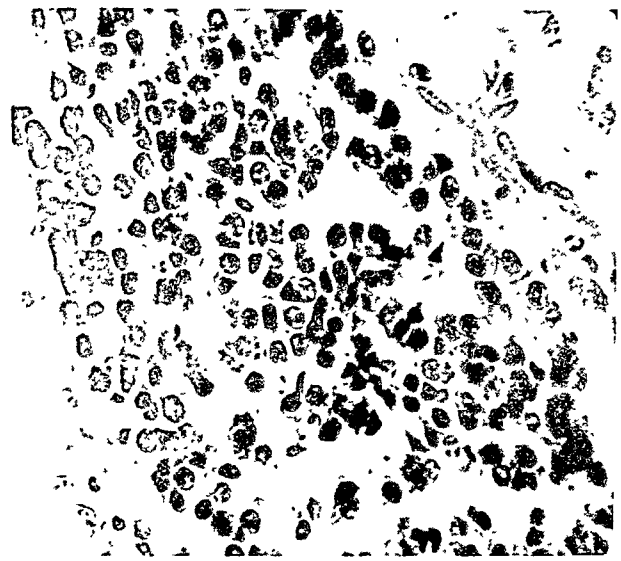


FIG. 2. A sheet of tumor cells under higher power. (Hematoxylin and eosin × 480.)

An intravenous pyelogram was negative. A gastro-intestinal x-ray series showed displacement of the second portion of the duodenum around the mass and retention of more than half the barium in six hours.

The patient was operated upon on October 29, 1945, under general anesthesia. The abdomen was opened through an upper right rectus incision. The right lobe of the liver and gallbladder were exposed and found to be essentially normal. The stomach and duodenum were normal.

The palpable mass was found to arise in the head of the pancreas. It was about the size of a small orange, was so well circumscribed that it seemed certain that it was not a malignancy. It was found that the tumor came very near the surface of the pancreas posteriorly. This portion of the pancreas was incised for a distance of about 2.5 inches. The tumor was dissected out and removed. A considerable number of large thin-walled, friable vessels passed from the pancreas to the tumor and bleeding was controlled with some difficulty. After a frozen section had been tentatively diagnosed as that of islet cell adenoma, the pancreas wound was approximated and the abdomen was closed, with a stab wound drain. Three 500 cc. blood transfusions were given during and immediately following the operation.

Blood sugar immediately following operation was 142, NPN 35. The following morning the blood sugar was 144, the icterus index 23 units. By the next day the icterus index was down to 5 units. Blood counts at intervals revealed only a polycytosis following operation. The patient was given Wangensteen suction, prostigmine every 6 hours, 30,000 units of penicillin every three hours, intravenous fluids with vitamin supplements, and dilaudid for pain. The Wangensteen tube was removed November 1, but the patient vomited his feedings and it was replaced. He continued to vomit feedings when the tube was removed and on November 9, a gastro-intestinal series showed almost all the barium retained in 6 hours and over half in 24 hours. Following this the patient was put on a regime of trasentin, intravenous fluids, and tube feedings, with aspiration of retention in 2 hours. The tube was removed on November 15 and a gastro-intestinal series showed satisfactory emptying of the stomach. The patient was discharged November 21.

PATHOLOGIC STUDIES

The specimen was a fairly firm, irregular, nodular mass with a definite capsule, measuring 7.5 × 7 × 5 cm. and weighing 165 Gm. The external surface showed many nodular structures varying in size from 1 to 2 cm. The fibrous capsule contained small blood vessels. The cut surfaces showed a lobulated appearance due to strands of fibrous tissue which seemed to enclose rounded masses of tumor tissue. In the center there was a firm, grayish yellow area measuring 2.5 cm. which on section proved to be gritty. The softer tissue in the rest of the mass was pinkish yellow, friable, and very finely granular.

On microscopic examination, the tumor was seen to be composed of cords and lobulated sheets of islet cells with fairly uniform round or oval nuclei and pinkish, granular cytoplasm. The shape of these tumor cells was polyhedral. The nuclei for the most part were vesicular and some showed one or two nucleoli. However, a number of the cells were pyknotic. There was a great tendency for the tumor cells, especially along the margin of lobulated groups of cells, to be arranged in rows, either straight or curved. They show no mitotic figures and were everywhere clearly demarcated from thin fibrous septa which separate them into lobulated masses, as shown in Figure 1. The stroma which made up the septa was hyalinized, collagenous fibrous tissue. In the center of the tumor, the hyalinized tissue had largely undergone calcareous degeneration.

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BOOK REVIEWS (Continued from Page 268)

To the physician who wishes to know more about disorders of metabolism than can be learned from the usual textbook of medicine, this book is highly recommended. It is a most valuable volume.

R. H. K.

PHARMACOLOGY, THERAPEUTICS, AND PRESCRIPTION WRITING. By W. A. Bastedo, M.D. 5th edition, 778 pages, illustrated. Philadelphia, Saunders, 1947. $8.50.

The author has attempted to modernize this textbook by including paragraphs on recently added therapeutic agents. The revision, however, does not seem to have proceeded beyond this goal. The chapter on digitalis which has been only slightly revised is still the most informative and best organized chapter in the book. The author's stages of anesthesia are fantastic and could have profited materially by editorial and factual assistance from a well-trained anesthesiologist. An unorganized attempt is made in scattered chapters throughout the book to teach the action of the autonomic drugs. If these drugs were discussed in a single chapter, which should be preceded by an accurate discussion of the anatomy, physiology and humoral transmission of nerve impulses (with diagrams of the autonomic system), greater clarity would ensue. The author apparently prefers "mouth dosage" to "oral dosage" but is still not consistent since he writes of "oral digitalization" which per se indicates the awkwardness of the term "mouth dosage." The illustrations of clinical reactions consist mainly of skin rashes produced by the various drugs while illustrations of the more serious reactions such as agranulocytosis, acute yellow atrophy, crystalluria, hemolytic anemia, and decreased renal function are omitted.

As a general principle one wonders if a textbook of this size and scope should attempt to include therapeutic procedures. These are best taught at the bedside in the presence of the carefully documented case history at which time all factors may be duly considered and evaluated.

C. C. PFEIFFER, M.D.

Cases from the Medical Grand Rounds of the Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.
BOSTON, MASSACHUSETTS

CASE 32

VITAMIN D POISONING

DR. EARLE M. CHAPMAN: This case is one of vitamin D poisoning. We think that this is of present interest because of the fact that vitamins have been advised so widely in the treatment of arthritis, particularly vitamin D concentrates, and also because in the last few years, we have come to recognize that a serious complication may arise from their use. At the American Medical Association meeting at Atlantic City this year there was a scientific exhibit on this disorder, and Slocumb's exhibit of 35 cases from the Mayo Clinic probably represented the largest series yet reported.

We are presenting a patient today who came in severely poisoned, who has improved, and is now much better, but who is not completely well.

Dr. DuToit will present this case.

DR. CHARLES H. DUTOIT: Mrs. W., No. 41092, is a 48-year-old married woman, who was in relatively good health until five years before the present admission. At this time she developed a mild arthritis, involving the left knee and then the right knee. She was admitted to the Phillips House in 1937, at which time her knee joint was explored and a torn cartilage taken out with some improvement of the left knee. However, the right knee continued to give her trouble, and she subsequently developed some limitation of motion and pain in the right wrist.

About two years before admission, she became so incapacitated that upon the advice of a friend, she began taking vitamin D capsules. They were 50,000 unit capsules, of which she took approximately six a day and sometimes more. She took these for roughly two years, stopping them in February 1947.

Her present illness began in January 1946 or a little over a year before her admission here. At this time, she stated that she began to feel tired, lost her "pep," sometimes was so weak that she couldn't carry out the things that she ordinarily had been able to do. Earlier she had been a very vigorous person.

In July 1946 she consulted her family doctor, who found a trace of albumin in the urine which apparently cleared up in a few days after forcing fluids. About November 1946 some six months before admission here, she had an episode of nausea and vomiting, which lasted for six days. At this time, the same doctor found her blood pressure slightly elevated. She was given a sedative and rest was advised, and apparently she returned to normal. She continued to feel weak, but managed to go about her usual activities, until one month before admission, or in March 1947. At that time she became nauseated and vomited to such an extent that she was unable to keep anything down becoming very dehydrated and was admitted to the Phillips House on April 12, 1947.

Upon admission she was pale and dehydrated; the thyroid was slightly enlarged, a finding which apparently had been present most of her life. She had a grade two apical and systolic murmur. There was limitation of motion of the right wrist with some limitation of motion of both knees, but not to a great extent. Her blood pressure was elevated, 185/100.

Dr. Chapman has the x-rays.

DR. CHAPMAN: All we can say about the x-rays is that they fail to show calcification in the kidney areas or any of the soft tissue deposits of calcium, as had been described in the cases. They do show slight widening of the cardiac shadow; and this was taken soon after entering. No calcification was seen throughout the lungs.

DR. DUTOIT: Urine on admission was acid with 2+ albumin, concentrated to 1.010 with 2 red blood cells and 100 white cells in the sediment. The urea clearance was 21 per cent of normal. An initial nonprotein nitrogen was 80 mg. per cent, which in three days became 45 mg. per cent. Serum calcium was 14.2 mg. per cent and phosphatase was 5.0 units per cent. Carbon dioxide, potassium and sodium were not remarkable.

On a regimen of intravenous fluid and forced oral fluid she continued with severe nausea and vomiting,

and appeared to be desperately ill for a little over two weeks. During this time, her calcium fluctuated as follows: It rose to 15.9 mg. per cent and then toward the end of April, two weeks after admission, it fell to 14.1 mg. per cent. The phosphorus tended to be below normal. Urine calcium excretion on the 15th of April, three days after admission, was 126 mg. in 24 hours. However, there was some doubt that it was a full 24-hour urine specimen that was collected. Subsequently, determinations were done on April 29th and May 7th, which were 201 mg. and 207 mg. respectively, slightly elevated values.

She continued to be very sick, until approximately the first day of May, when she improved dramatically. By the 15th of May her blood calcium had fallen to 11.2 mg. per cent but the phosphorus remained low at 2.2 mg. per cent. She was discharged on May 15th and was able, by that time, to eat a full diet without distress.

DR. CHAPMAN: Before showing this patient, I should like to highlight the history. This woman had arthritis, and took large doses of vitamin D because a relative had been to a clinic and was advised to take vitamin D for her arthritis. She calculated her own dosage on the strength of what had been recommended to her sister.

I want to give credit to Dr. Sidney Derow, her family physician, who recognized this problem in the spring of 1946 at which time he urged her to give up vitamin D. She did not do so, because it had done the arthritis "so much good." Later he again urged her to give it up. When she became ill, with constant vomiting, and had the appearance of uremia, he was the one who made the diagnosis of vitamin D poisoning.

This woman presented a great problem in therapy because of peculiarities of her personality. She believed, I think, in various forms of healing other than the regular medical arts, had a great fear of needles, and absolutely refused to have any needles put into her. She continued in this attitude during the first few days in the hospital until after Dr. Bauer's helpful consultation, which consisted of the two of us pounding on the bedside and insisting that she take the treatment or go home, as we had nothing else to offer. She took the treatment, consisting of parenteral fluids for two weeks, which we think changed the downhill course and brought her out of uremia.

Mrs. W. says that she now feels very well and has resumed household duties of a moderate nature. She has continued to have nocturia about twice and as you see she has pitting edema of the lower extremities. She is unable to wear ordinary shoes and wears only sandals. As you see her this morning, she is the picture of health; she has gained 13 pounds in weight: her blood pressure this morning is slightly elevated, 160/90, but she is doing very well.

There were two diagnoses that entered into the differential diagnosis of this case. One was that it was hysterical vomiting, with secondary alkalosis, and so-called "achloremic uremia." The finding of normal serum chloride and CO_2 pretty well excluded that. The next point was the exclusion of hyperparathyroidism because of the finding of a high blood calcium and low blood phosphorus. Dr. Albright saw this patient and wanted to be sure. We have the skeletal x-rays, which showed no evidence of abnormal calcium deposits.

DR. WALTER BAUER: How did he explain the hypophosphatemia?

DR. CHAPMAN: I don't know. As the calcium goes up, the phosphorus usually goes down. I don't know any other way to explain it. The calcium was low the last time, and when the calcium was nearer normal, the phosphorus was still low. We have taken calcium and phosphorus and NPN and other things this morning, but of course we haven't the reports yet.

The next point that I would like to review is that of the salient features, from the experience of Slocumb's review of 35 cases that he showed in an exhibit at the American Medical Association meeting. Probably they apply here. He found the serum calcium varied from 11 to 16 mg. per cent and returned to normal in one to eight months. In this patient, the return to normal was much more rapid than we had anticipated. At the end of one month she was down to a little over 11 mg. per cent. The anemia seems to be the outstanding feature of these patients. Slocumb found that 71 per cent had anemia. This woman had 12.2 Gm. on admission but by discharge had fallen to 9.7 Gm. She had had, I think, two transfusions in that interval, as well as a trial of iron therapy.

DR. BAUER: If I might interrupt, it is only fair to say that we mustn't lose sight of the fact that anemia is a common finding in rheumatoid arthritis. I don't think we should emphasize the anemia too much as necessarily being a manifestation of vitamin D intoxication.

DR. CHAPMAN: I agree with you.

DR. WYMAN RICHARDSON: It is common in uremia, too.

DR. CHAPMAN: In their experience they found that if the kidney damage existed as long as six months it was considered irreparable and would go on to chronic renal damage. This patient still has evidence of damaged kidneys, I would say.

The next thing is that the calcium deposits continue to be absorbed up to the seventh month; the absorption of the calcium deposits in the kidney that caused the injury primarily may be repaired in whole or partly up to the seventh month, but after that time, very little further absorption occurs.

DR. MAURICE FREMONT-SMITH: Was she constipated before becoming acutely ill, as so often happens in calcium poisoning?

DR. CHAPMAN: Constipation was present and was severe during the illness. She hadn't ordinarily been constipated before that.

There is one other point that I think is of importance. Her dosage was somewhere in the region of 200,00 to 300,000 units of vitamin D, given in the form of Doral, a proprietary preparation. As you know, from the recent published report in the Journal of American Medical Association, fatal outcome has been described with doses as low as 50,000 units daily, over a period of a few months (Kaufman, P., R. D. Beck, and R. D. Wiseman, J. A. M. A., 134:688, June 21, 1947). So that the dosage factor, the high dosage factor, is not always important. In Slocumb's experience I think it was found that the greatest number of patients had received in the neighborhood of 100,000 units which had led to poisoning; some had been as low as 50,000 and in only a few, as high as 300,000.

Dr. Bauer is here, and I would like to have him comment on this case. Perhaps Dr. Mallory would like to say a word first.

DR. TRACY B. MALLORY: I haven't much to say. My experience with this condition is very limited. We had a case which came to autopsy a few months ago, but death could not in any way be attributed to the hypervitaminosis, inasmuch as the case was slightly complicated with Hodgkin's disease and miliary tuberculosis.

The kidneys, however, did show very marked deposits of calcium, which were found in the pyramids, lying in the interstitial tissues, just external to the tubules. There were no casts of calcareous material in the tubular lumens. The picture is, to my eye, essentially similar to that which is seen in the kidney with hyperparathyroidism, and also in occasional cases of severe, prolonged alkalosis. I do not believe I could differentiate from the slides of the kidney, between the various causes of the calcification. In the case just referred to, the kidney was the only organ to show the metastatic calcification. We did not find calcification in the blood vessels, or in the alveolar walls, as one may find in severe cases of hyperparathyroidism or of chronic nephritis.

DR. BAUER: The primary pathologic process was in the tubules?

DR. MALLORY: Very probably but I couldn't say it was from the findings at the time of autopsy. The calcification was interstitial then.

DR. BAUER: The glomeruli and tubules were normal?

DR. MALLORY: It may have been deposited originally in the tubules and the calcareous material subsequently extruded. At the time of postmortem, all the calcium was outside the tubules. In hyperparathyroid cases, the same thing has been true.

DR. CHAPMAN: Dr. Bauer, would you comment on this problem?

DR. BAUER: In 1938, we reported our experience with large doses of vitamin D in the treatment of rheumatoid arthritis (Abrams, N. R., and W. Bauer: Treatment of rheumatoid arthritis with large doses of vitamin D: a critical evaluation, J. A. M. A., 111: 1632–1639, October 1938). Our observations, though limited to 18 patients, indicated that the administration of massive doses of vitamin D in rheumatoid arthritis is of little or no value in altering the course of the disease. Subjective improvement lasting throughout the period of therapy was observed in only eight cases. In three instances there was accompanying objective improvement. In only one was it marked. The beneficial results in this last instance as in the others was shortlived. During the follow-up study, it was noticed that the arthritis gradually became as severe as it had been in the pre-treatment period. Such changes were obvious in a few weeks. The other patients who had experienced subjective and objective improvement fared no better. In 14 cases not materially influenced by vitamin D, the arthritis ran the same pre-treatment course during and after the period of administration of vitamin D. Thus, it was concluded that the general effects of the larger doses of vitamin D do not appear significantly different from those observed with the usual therapeutic doses and do not justify the expense and dangers involved.

The dangers associated with this form of therapy are real and, therefore, I call them to your attention again. The most serious effect from vitamin D intoxication is the hypercalcemia which, if allowed to persist, results in extensive calcium deposition and other pathologic changes.

In our study, pre-treatment calcium, phosphorus, and phosphatase values were obtained. These determinations were repeated at weekly or bi-weekly intervals throughout the period of vitamin D therapy. In 16 of the 18 patients, hypercalcemia developed at some

time during the period of treatment. In nine of the 18 patients, it was noted on only one or two occasions. In five instances, there were no significant associated symptoms of toxicity and the serum calcium returned to normal without alteration of the dose of vitamin D. In four other cases, vitamin D was discontinued or the dose was reduced because of the degree of hypercalcemia or the severity of the toxic symptoms. In seven patients, fasting serum calcium values varying from 11.2 to 16.0 milligrams per hundred cubic centimeters persisted for weeks (from three to twenty-five), unless the dose of vitamin D was reduced or the drug discontinued. In most instances, such values for hypercalcemia were not encountered until the dose was maintained between 160,000 and 200,000 U.S.P. units daily. However, a hypercalcemia of from 11.2 to 14.2 milligrams per hundred cubic centimeters was observed in one patient for a period of 25 weeks, during which time the daily dose of vitamin D never exceeded 60,000 U.S.P. units. We were unable to exceed a dose of 200,000 U.S.P. units daily of crystalline vitamin D in propylene glycol administered in milk without encountering toxic symptoms.

The toxic symptoms observed were similar to those previously described, consisting of anorexia, nausea, vomiting, epigastric distress or pain, diarrhea, headache, drowsiness, polyuria, polydipsia and nocturia. In some instances, these symptoms were sufficiently marked to be alarming. Both the toxic symptoms and hypercalcemia often persisted for several weeks following discontinuance of the vitamin D therapy. An increased fasting serum phosphorus was observed on only two occasions. In these two instances, values of 5.1 and 5.5 mg. per cent were observed with serum calcium values of 11.3 and 16.6 mg. In only one case did the serum phosphatase rise above a value of 5 Bodansky units. The value in this single instance was 6.5 units, with a normal serum calcium and phosphorus. The degree of hypercalcemia, its duration, and the severity of the associated toxic symptoms were in no way related to the observed subjective and objective changes.

From our experience, it is evident that the dangers of vitamin D poisoning far outweigh the therapeutic result the patient will obtain. It is for this reason that we do not advocate its use in the treatment of rheumatoid arthritis. If one employs it, he must be continually aware of the possibility of producing serious pathologic lesions, some of which may be irreversible. Renal insufficiency, with or without renal stones, and calcification of the periarticular tissues are the lesions most frequently encountered.

Dr. Chapman's patient has a hypophosphatemia. This has been observed in other cases of vitamin D poisoning, as was reported recently by Dr. Slocumb. Its exact cause is unknown. Can it be an expression of a secondary hyperparathyroidism? If so, what is the mechanism of production? Will it subside completely? Perhaps Dr. Aub will comment on this interesting feature of this patient's disease.

The renal lesion which is thought to be due to calcification of the interstitial tissue may be reversible, but not as regularly so as we sometimes wish. In some patients with vitamin D poisoning, one may find extensive calcification of the periarticular tissues. Such calcium deposition may disappear completely once the patient recovers from the vitamin D intoxication. I hope Drs. Aub and Mallory will comment on this aspect of vitamin D poisoning. As they probably know, such extra-articular deposits may disappear within six to eighteen months.

DR. FREMONT-SMITH: Was there any evidence of therapeutic value, as far as the arthritis was concerned?

DR. BAUER: In this clinic, no.

DR. JOSEPH C. AUB: I don't understand what you meant about the deposition of calcium. When did it occur?

DR. BAUER: In this case, it did not occur. In some cases reported by Dr. Slocumb there was considerable calcium deposition in the periarticular tissues of one or more joints; yet, it disappeared completely.

DR. AUB: When will it disappear?

DR. BAUER: In a matter of six to eighteen months.

DR. AUB: With or without the vitamin D?

DR. BAUER: Without the vitamin D. In what form is this deposited and why can it be re-absorbed?

DR. AUB: Of course, it is obvious that if Dr. Bauer asks me any questions on this subject, I can't answer them. I would like to comment on this case. First of all, on the relationship of the nephritis; secondly on the time relationship of the effects.

About five years ago, I showed a patient at one of these clinics and I think the first example of the effect of a high blood calcium in producing a nephritis. In other words, that something within one's self might produce a nephritis which was reversible.

At that time, I showed a boy who had had a blood calcium of 19.6 mg. per cent with hyperparathyroidism in which the considerable evidence for nephritis had vanished after the hyperparathyroidism had been corrected. When I demonstrated him, he was in the army and then he was beginning to show hypertension. Ten years after cure of the hyperparathyroidism there proved to be a definite residual of his nephritis. I suppose the nephritis which comes from this hyper-

vitaminosis also comes from a high blood calcium and has nothing to do specifically with vitamin D.

The second thing that interests me very much is the duration of these effects. It takes parathormone four hours to influence blood levels which then last 20 hours. Vitamin D doesn't produce hypercalcemia, even if you give huge doses, except after a matter of days, usually a week; then the hypercalcemia continues to exist, after you stop the vitamin D, in fact the hypercalcemia may rise for some time after the vitamin D is stopped, and then does not subside for many weeks. Now that practically rules out, I think, one of the questions that Dr. Bauer asked, whether it was due to a secondary hyperparathyroidism. The duration of these effects imply that vitamin D alone is involved and not the parathyroid.

DR. BAUER: I do not agree with you. I don't see why four hyperplastic parathyroid glands should come back to normal in a matter of days. I should think it would take weeks or months, after discontinuing therapy.

DR. AUB: It is my recollection that these hypercalcemias which come on with vitamin D do not have a hypophosphatemia.

DR. BAUER: They do.

DR. AUB: I would think this is a very unusual one.

DR. BAUER: There are others on record, the biggest series is that of Slocumb.

DR. AUB: The answer is that Dr. Bauer and I disagree and neither one of us can arrive at an established conclusion now.* I have evidence on early observations of blood calcium and phosphorus, with the giving of huge doses of vitamin D, but that was accumulated so long ago that I cannot be sure of my memory. Hypophosphatemia did not occur, I believe. Blood phosphate level is probably the real answer to the problem.

Follow-up Note

No follow-up data are available on this patient except the reports of calcium and phosphorus as of July 10th: Calcium 10.8 mg. per cent and phosphorus 2.6 mg. per cent.

CASE 33

MYELOGENOUS LEUKEMIA

DR. WYMAN RICHARDSON: We feel that this patient does not present a problem in diagnosis, but we are presenting her in order to discuss therapy and also because I would like to discuss allied conditions.

Dr. Friedlich will present the case.

DR. ALLAN M. FRIEDLICH: Mrs. S., No. 581648, is a 51-year-old housewife, who entered the hospital on July 14, 1947 because of one week of chills and fever. Her present illness began one year ago, at which time she started to lose weight, from her usual 178 pounds, down to 148 pounds six weeks ago. Her appetite during this period was fair. She was not on any self-imposed diet, and had no other gastro-intestinal symptoms. Six months ago, she noticed fatigue and because of that condition consulted her local physician, who started her on a series of injections of vitamins and, evidently, estrogens because of the concomitant menopause. During this time, she felt somewhat better and was able to return to her household duties. However, two months ago, she noted some twinges of pain in the left upper quadrant; on palpating herself in this area, she discovered a firm, nontender mass just below the left costal margin. This mass at first grew slowly, but grew more rapidly latterly.

Two months ago, she also had her first and only episode of bleeding, which consisted of a nose bleed, intermittently for several days. One week prior to entry she had a chilly sensation, followed in two days by frank chills and fever up to 105°.

She was admitted to another hospital, where she received one blood transfusion and was transferred here. On admission here, she was an acutely ill woman, sweating profusely, with a temperature of 104° by mouth and a pulse of 104. The only palpable lymph nodes were two small ones in the postauricular area. The chest was clear and the heart was not enlarged. There was a grade three apical systolic murmur, transmitted over the entire precordium, but not to the upper vessels of the neck, or the lung bases. The liver dullness extended from the fourth rib anteriorly, 6 cm. below the right costal margin, where a firm, nontender liver was palpable. The spleen was markedly enlarged, descending to the iliac crest; it was smooth, and likewise nontender. The remainder of the physical examination was normal. The urine was normal. The hemoglobin was 7.4 Gm. and the red blood cell count was 3.2 million. The white blood cell count was 340,000. Dr. Richardson will describe the smear.

DR. RICHARDSON: The patient says she is better today and has no pain. She had liver extract. Just what was it she had, do you know?

DR. FRIEDLICH: We don't know the nature of the injections.

DR. RICHARDSON: I understand it was liver anyway. She was given it "by needle" twice a week for about four months and she says it did make her stronger since before that she couldn't even hold a cup. Since the injections she can at least get the children's meals and do some dishes.

* Editor's Note: From a review of the literature, it appears that the phosphorus values in this illness are not as consistent as are those of calcium. Cases of toxicity have been reported with low, normal, and elevated phosphorus values.

The blood picture is about what one would expect. There were many, well-differentiated neutrophiles and there were a few stem cells which one could call myeloblasts. I called them that because I could recognize the myelocytes with which they were associated. I think there is no reason to doubt the diagnosis in this case of chronic myelogenous leukemia occurring at the age where this disease is commonly seen, and of relatively short duration.

In commenting about the treatment, there is one point that I should like to make first and that is, that these patients frequently do have a history of some bleeding. This patient had a rather minor nose bleed. Frequently patients have teeth removed, probably mistakenly, and frequently they bleed a great deal from the removal of the teeth. The cause of the bleeding is not entirely apparent, or perhaps not at all apparent. It is not due to platelet lack, because this patient has, as most of them do have, greatly increased platelets. There may be an increased prothrombin time. The bleeding is described as due to what is called leukemic infiltration. I don't know just why that produces bleeding.

As you know, these patients also have a considerably increased basal metabolic rate. They commonly show evidence of vitamin deficiency, if tongue changes are taken as such evidence, in much the same way that the patient with polycythemia may show evidence of vitamin deficiency, as well as patients with thyrotoxicosis.

It is true that the use of liver extract in this type of individual is often associated with considerable clinical benefit. I have assumed that to be due, probably not so much to the giving of the liver principle, although that may have some bearing, as there may be a secondary lack of liver principle in these patients, contributing towards the general picture. It may also be that the liver extract contains a considerable amount of some of the factors that go into the vitamin B complex. In any case, some of these patients do get considerable benefit from liver parenterally.

The standard methods of treatment include radiation, directed either toward the spleen or radiation by means of spray, that is, radiation to the entire body. Or, there is also the use of irradiated phosphorus, irradiated isotopes or the use of arsenic.

I think that most people, except perhaps Forkner himself, have given up the use of arsenic, for the reason that in order to get a response with arsenic you have to poison the patient, and you are left with a patient that not only has myelogenous leukemia, but also has the symptoms and often the signs of chronic arsenic poisoning. Most of us have felt that it did not do anything which radiation could not do, and that arsenic would not produce a remission if radiation would not.

The question is this: If you then believe that radiation is the treatment of choice, what type of radiation should you use?

I want to say that I have seen such patients over a considerable period of years now—not a great number of them, but quite a few, and I get the following impression: If you irradiate these patients in a generalized way, they succumb more rapidly to anemia than if you irradiate the spleen locally. That would seem to me to be a reasonable supposition, because in this hospital we treat polycythemia vera with spray radiation and by so doing greatly reduce the red blood cell count. It is my feeling, therefore, that if you use spray radiation or irradiated isotopes, the result is that the patient dies more quickly and that anemia develops more surely and more quickly than if you radiate locally. Therefore, I believe in radiation of the spleen alone.

You might ask why it is that radiation over the spleen alone will produce a remission, as it will in this patient I am sure. I don't know the answer. I have often wondered about it. I have some rather wild theories and one of them is that these cells that are in this patient's blood are hungry, so to speak, and are not getting the right substances for normal maturation and perhaps by radiation locally over the spleen, where there is a great body of cells, enough cells may be destroyed to supply these food factors for the remaining cells. Some people have the feeling that the radiation effects can be transmitted from the spleen to the marrow. However you wish to explain it, the fact remains that remissions can be produced constantly in these patients, if they are treated early. The remission may not be produced every time after that, of course, because these patients do die eventually, perhaps in four years or so, after the diagnosis is established.

This patient has had radiation to the spleen, beginning with 75 R. The next day she had two treatments, one of 75 R and one of 25 R or a total of 175 R over the spleen. Her temperature appears to be coming down. She has been running a jagged, high fever. It is not as marked now as it was, and, clinically, the patient appears to be better. It looks as if she would require not very much more treatment, perhaps 400–500 R will be sufficient to put this patient into what would be a relatively complete remission, and it will be anybody's guess as to how long that remission will last.

I have a patient whom I saw just a few days ago, who illustrates what I think is the most important

point in regard to therapy of these patients. It is this: When shall we treat this patient again? How long shall we let the leukocytosis build up before we treat it? What are the criteria for further treatment? I think the important dictum is this—that you want to treat the patient and not the blood picture.

The office patient about whom I was speaking had his last x-ray treatment for myelogenous leukemia in June 1946, and in the spring of 1947 his white count began to rise. It had reached 120,000 in May, but the patient himself said that he felt better than he had for years. His spleen at that time was four fingers below the costal margin and Dr. Robbins and I decided, although the count had suddenly spurted up, that we would not treat the white count, but that we would treat the patient: Therefore we did nothing.

In June the white count had reached 150,000 and the patient was still feeling fine; the spleen was three fingers below the costal margin. The last time I saw the patient, early this month (July), the white count was 140,000 and the patient was still feeling very well and the spleen was only two fingers below the costal margin. The patient appears to be having a spontaneous remission. He illustrates clearly, to my mind, the point that these patients should not be treated by radiation on theoretical grounds, as far as the count is concerned, but should be treated in connection with their clinical symptoms.

I feel very strongly that there are a limited number of x-ray treatments which are going to be beneficial, and they should not be used up any more quickly than is necessary. In other words, radiation should be put off as long as possible. I realize that that goes against the theory that others have had, which is that you ought to hold the disease in check the minute it begins to show any evidence of increased activity. I think that that is the wrong point of view.

So in summary, I feel that the best form of treatment which this type of patient could receive is radiation to the spleen, given in small doses, just as small doses as one can get away with, and at as infrequent intervals as possible.

I want to discuss a related condition, but first I shall ask if anyone wishes to discuss this particular case? Dr. Bauer, is there anything that you would like to say?

DR. WALTER BAUER: Why do you think radiation releases something the other cells need? What is responsible for the increased number of cells? Is it not necessary to account for the latter before postulating regarding the nutritional requirements of the cells?

DR. RICHARDSON: There are more cells because they lose the power of differentiation. If they lack a certain substance, but do not lose the power of reproduction, then the reproduction is an attempt to reach a differentiating point. That is pure theory. If you want to compare it with a known condition, you may compare it with pernicious anemia: The red cells have not lost their power of reproduction but have lost their power of differentiation.

I feel very strongly that the attempt to destroy cells is the wrong approach to the field of malignant disease. I don't think we ought to try to kill them all. They are sick and we ought to try to cure them and make them well, and by trying to kill them all the time we will never get anywhere.

DR. BAUER: You want to make them grow up!

DR. JOSEPH C. AUB: I like what Dr. Richardson said. You say you don't destroy the cells and you want to prevent destruction. Well, urethane ought to do that. While it isn't terribly good, I think it is worth a try in all of these chronic leukemias, because it inhibits cell division and therefore it is a more logical method of therapy.

Of course we all agree that the x-ray can be used a certain number of times, and then it stops being of value. I think that there is a gradual crescendo toward a greater and greater degree of malignancy.

DR. FREMONT-SMITH: Would you say a word or two about urethane, so that we will know what it is?

DR. AUB: It is ethylcarbamate. It was a drug that we formerly used in physiology as an anesthetic. It was studied by Dustin and determined to be one of the best inhibitors of cell division that he found, colchicine being another example. Urethane works particularly well in inhibiting leukemic cell division, according to Haddow. It was first reported in *Nature* in April 1946 (Haddow, Alexander, and W. A. Sexton: Influence of carbamic esters (urethanes) in experimental animal tumours, Nature, 157:500–503, 1946) and also in the British journal, *Lancet,* in May 1946 (Paterson, Edith, I. A. Thomas, A. Haddow, and J. M. Watkinson: Leukemia treated with urethane compared with deep x-ray therapy, Lancet, 1:677–683, May 11, 1946). Cases of leukemia were presented in which the white count fell and remained down for several years, merely by the giving of urethane by mouth, in amounts not sufficient to cause analgesia.

There are two characteristics of importance in neoplastic cells. One is that malignant cells are empty cells. That agrees with Dr. Richardson's views. The other one is sustained cell division. When it comes to leukemia, you know a fair amount about it, for an adult cell lives four days, and the speed of cell division of white cells is enormous.

DR. BAUER: What is the length of life of a myelocyte?

DR. AUB: I am not sure, but the total amount of di-

vision is tremendous. A normal white cell only lives four days in the circulation. If there is an increase from 4,000 polymorphonuclear cells to 100,000, which may occur in a few hours in infection, you may calculate the terrific number of white cells that are produced. It isn't the speed of the division which is abnormal in leukemia, it is the fact that they continue to divide—that rapid division is sustained for long periods of time.

DR. RICHARDSON: In regard to urethane, I agree that we could try it in this patient. I know of one who has had urethane and I thought there was a rather indifferent result there. Dr. Kennedy may have seen her more recently, but the last I heard she was not doing so well with urethane.

DR. AUB: But occasionally they do well.

DR. RICHARDSON: The other thing that I was going to discuss was the relationship between leukemia and what some are pleased to call agnogenic myeloid metaplasia. The original report by Parker and Jackson (Jackson, H., Jr., F. Parker, Jr., and H. M. Lemon: Agnogenic myeloid metaplasia of spleen; syndrome simulating other more definite hematologic disorders, New England J. M., 222:985–994, June 13, 1940) included two or possibly three conditions which I would call something different. The first one is bone marrow encroachment, with extramedullary blood formation. That is the commonest cause of splenomegaly in the older age group. It is due to bone marrow invasion by carcinoma, with the spleen taking over the marrow process, and enlarging greatly, producing a very hurried and therefore somewhat abnormal blood picture. The crux of the blood picture is that the red cell regenerative picture is very great, with all kinds of nucleated cells, polychromes and so on, whereas the white cell picture is relatively normal with perhaps a few myelocytes, usually the late type. The white cells of the neutrophilic series are usually pretty well differentiated, compared to the undifferentiated red cell picture.

The second disease which they described was think, hemolytic anemia, associated with mal gnar We know that it occurs very rarely. In the original group, there are one or two cases that seem to fall into that category. Possibly there is a third group. We have seen patients with a picture which is indistinguishable from myelogenous leukemia. One might well say that these patients have carcinoma and, also, myelogenous leukemia. By and large, most of these patients have bone marrow encroachment and extramedullary blood formation in the spleen.

The cases of polycythemia treated by frequent blood letting, almost invariably end up with myeloid metaplasia. But in this hospital, where nearly all cases of polycythemia are treated with spray radiation, we haven't had a single case of myeloid metaplasi ir '5 years. One private patient, having had polycythemia vera for 11 years, which has been treated by four courses of spray irradiation, is, I believe, now in the Baker Memorial with "acute leukemia."

I would prefer to use the words "bone marrow encroachment, with extramedullary blood formation."

Editor's Follow-up Note

This patient was given a total of 575 R over the area of the spleen. There was marked subjective and objective improvement in her general status at th termination of the course of treatment as manifested by a flat temperature curve, good appetite, decrease in size of the spleen, and a marked decrease in tota white count. The last white count on the 30th of July, the day before discharge from the hospital, was 22,000. The patient was followed at monthly intervals in August, September, and October, on each of which visits it was recorded that she felt very well and had gained 23 pounds since discharge. On the 6th of October, her total white count was 16,600, with only two abnormal cells recorded in the smear. Her hemoglobin was up to 12.4 Gm.

Diagnosis of Case on Page 255

CLINICAL DIAGNOSIS

Subacute bacterial endocarditis due to Streptococcus viridans.
Rheumatic heart disease, mitral and aortic insufficiency.
Embolic nephritis. Secondary anemia.

PATHOLOGIC DIAGNOSIS

Acute ulcerative endocarditis of mitral and aortic valves. (In addition to vegetations on the leaflets of the valves, one leaflet of each valve had an ulcerated perforation.)
Stenosis of the aortic and mitral valves.
Chronic passive congestion of lungs with bronchopneumonia and embolic pneumonia.
Embolic nephritis.
Infarction of jejunum, spleen and kidney.

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